

INTERNATIONAL
RARE DISEASES RESEARCH
CONSORTIUM

**State of Play of Research
in the Field of Rare Diseases:
2012-2014**



IRDIRC

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IRDiRC can be found at www.irdirc.org

Disclaimer:

The report is a presentation of the current literature, organised in order to identify and highlight trends and breakthroughs in research in the field of rare diseases. The report does not focus on initiatives to improve the organisation of healthcare systems or on articles covering aspects of the orphan drug market. In addition, trends and breakthroughs in genomics, and -omics in general, are not reported unless they bear specific rare disease features.

The report is based on published articles, therefore a time lapse between scientific breakthroughs and their publication is inevitable and the report may not perfectly reflect the initiatives at the time at which they are launched.

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EXECUTIVE SUMMARY

Introduction

The International Rare Diseases Research Consortium (IRDiRC) was established in 2010 to associate researchers and organisations invested in rare disease research in order to achieve two main objectives by the year 2020, namely to deliver 200 new therapies for rare diseases and means to diagnose most rare diseases.

Methods

This report is a compilation of information published in scientific journals over the past two years. The scientific literature was systematically scanned using the key words “rare diseases” and “orphan drugs” and their synonyms. In addition, the summary tables of forty top ranking journals in various fields were systematically scanned.

All the articles describing major initiatives or major research outcomes were selected and highlighted in an electronic newsletter, *OrphaNews*, which also publishes news about specific rare diseases. Only the articles tackling a general issue, not disease specific, were retained for this report.

This material was organized under two main topics: Initiatives and Trends & Gaps. The focus remains on the two IRDiRC goals. Therefore initiatives to improve the organization of the healthcare system and articles dealing with the economic aspects of the orphan drug market were not considered.

The report does not necessarily reflect the opinion of the IRDiRC members, but the analysis of the scientific secretariat through the conducted literature survey.

I. RECENT INITIATIVES TAKEN TO SPEED UP R&D

1 Recent initiatives taken to speed up R&D in Europe

1.1. Initiatives in the EU to reduce the attrition rate of Orphan Medicinal Products during the R&D process

The European Medicines Agency (EMA) took the initiative to encourage small- and medium-size enterprises (SMEs) to seek scientific advice to increase their chances of market authorization (MA). The EMA provides a number of financial and administrative incentives to SMEs to help them obtain MAs for their medicinal products. A report published by the EMA in 2013 has shown that although the number of MA for SME-developed medicinal products has increased over the past seven years, it is still lower than *“the average for all applicant companies”*. The EMA suggested that many SMEs would benefit from seeking scientific advice at an earlier stage of development. To increase the chances of market authorizations for SMEs, the EMA *“...encourages SMEs to approach the SME office to discuss the certification process and overall regulatory support available to them”*.

1.2. Initiative in the EU to reduce the administrative burden linked to the regulatory process

In 2013, the EMA decided not to require sponsors of medicines who have received orphan designation to inform the agency of their intent to apply for fee reduction eligibility. In an effort to reduce the administrative burden on the EMA, they have cancelled this procedure and have said that they no longer *“need additional information from the sponsor before submitting an application eligible for fee reduction orphan medicines”*.

1.3. Initiative in the EU to improve safety and efficacy of orphan medicinal products

As part of its pharmacovigilance activity, the EMA published a report on medicinal products in the European market that require additional monitoring. The highlighted medicinal products on the list are orphan products under further examination. This document is crucial for rare disease patients and their clinicians, allowing them to be continually vigilant and apply safety and efficacy measures to report adverse events promptly.

1.4. First candidates selected for EMA’s adaptive licensing pilot project¹

Following the launch of the EMA’s adaptive licensing pilot project in March 2014, the agency has selected two products from the twenty applications received from companies. While the medicines have not been publicly revealed, the agency will contact the selected applicants in order to begin exploring potential adaptive licensing for these products. The EMA welcomes the rapid response and growing interest from companies to engage in the pilot project. The greater the number of projects, the more evidence regulators can gather to validate the

¹ EMA news release: European Medicines Agency selects first two medicines to be included in its adaptive licensing pilot project
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002119.jsp&mid=WC0b01ac058004d5c1

adaptive licensing project. Adaptive licensing aims to improve early access to new drugs for diseases with unmet medical needs. Data for benefit/risk assessment will be collected progressively to establish safety and efficacy of medicines, with a view to treat a wider patient population. Built on multi-stakeholder cooperation, the EMA's adaptive licensing represents a further effort to speed up the design of products and treatments based on concrete evidence.

1.5. EMA offers further fee reductions for orphan drugs²

In December 2013, the EMA announced greater fee reductions for large companies planning to market orphan drugs for rare diseases in the EU, as a further incentive for orphan medicinal product development. Changes will take effect in 2014, extending reduced regulatory fees to large companies, besides micro-, small- or medium-sized enterprises (SMEs). Larger non-SME companies, submitting a marketing application for an orphan drug, will be eligible for a 75 percent fee reduction for non-pediatric related initial and follow-up protocol assistance. Previously, larger firms benefitted from a 40 percent reduction only. The EMA will also introduce a 10 percent fee reduction for initial marketing-authorization applications that currently offer no reduction. A 100 percent reduction will be applied to pre-authorization inspections where no fee reduction is currently offered. These incentives intend to encourage pharmaceutical companies to enter the growing rare disease market which drug makers have tended to avoid due to its limited market size. In addition to the fee reductions for larger companies, the EMA also confirmed current financial assistance for SMEs. This includes free-of-charge services for all initial and follow-up protocol assistance, initial marketing-authorization inspections and pre-authorization inspections. Other incentives for orphan drug developers in the EU include ten years of market exclusivity and the possibility to submit a single marketing authorization application to the EMA.

1.6. Initiative from the EMA regarding drug data to address HTA needs: a three-year joint work plan is established³

The EMA has agreed to a three-year joint work plan with EUnetHTA, which represents health technology assessment (HTA) bodies across Europe, in efforts to harness its relationship with national bodies such as the UK's National Institute of Health and Care Excellence (NICE) that assesses drug cost-effectiveness. Improving collaboration is key to this plan: it must facilitate the EMA's benefits and risks assessment for medicines' approval in the EU, whilst satisfying HTA agency requirements concerning approved medicines' suitability for national reimbursement. The need for extended scientific advice and early dialogue between the EMA, HTA bodies and pharmaceutical companies was further highlighted in the plan. The plan stipulates that ideas should be exchanged to develop scientific and methodological guidelines to facilitate clinical-trial design that can generate data relevant to both parties.

² EMA news release: European Medicines Agency applies greater fee-reduction rates for orphan medicines in 2014

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/12/news_detail_001984.jsp&mid=WC0b01ac058004d5c1

³ EUnetHTA-EMA press release: European Medicines Agency and EUnetHTA agree joint work plan

<https://eunetha.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/EMA-EUnetHTA%20press%20release%20-%20final%20version.pdf>

Additionally, collection of post-authorization data, once the drug is on the market, and specific ways to share information on orphan drugs for rare diseases are also included in the plan. This publication is part of a collaborative effort between the EMA and EUnetHTA, initiated in 2010, addressing recommendations made by the EU's Pharmaceutical Forum – a group comprising members from EU Member States, EU institutions, industry, healthcare professionals and patients.

1.7. Initiatives in the EU to develop new methods to design and analyze clinical studies in rare diseases

The European Commission awarded grants to three European projects dedicated to methodology issues linked to small population studies.

- ▶ **ASTERIX⁴ (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence)** is an FP7 EU-funded research project (from 2013 to 2017) designed to optimize methodology for clinical trials in small populations to achieve more reliable and cost efficient clinical development of treatments for rare diseases. Key methodological innovations include new standards of evidence that take into account the rare prevalence of disease. Such methods facilitate adaptive design and sequential meta-analysis, using multiple endpoints, and provide a blue print to pro-actively share information on trials in the planning stage. ASTERIX will systematically involve patients in the research process and their input will be taken into account in study design and analysis.
- ▶ **IDEAL⁵ (Integrated DEsign and AnaLysis of small population group trials)** is an FP7 EU-funded research project (from 2013 to 2016) which will focus on assessing randomization procedures, extrapolating dose-response information, optimal designs in mixed models, pharmacogenetic designs, simulation of clinical trials, and decision analysis and biomarker surrogate endpoints.
- ▶ **INSPIRE⁶ (Innovative methodology for Small Populations Research)** (from 2014 to 2017) will focus on early phase dose-finding studies in small populations, decision-theoretic methods for clinical trials in small populations, and the use of evidence synthesis in the planning and interpretation of clinical trials in small populations and rare diseases.

1.8. Initiative in the EU to increase clinical trial transparency⁷:

Under a draft law unanimously agreed upon with EU ministers and passed by Parliament on April 2nd, 2014, pharmaceutical companies and academic researchers will have to post results from all their European clinical trials in a publicly-accessible database. This is necessary to increase transparency in order to build trust and confidence. These trials must

⁴ ASTERIX (Advances in Small Trials dEsign for Regulatory Innovation and eXcellence) <http://www.asterix-fp7.eu/>

⁵ IDEAL (Integrated DEsign and AnaLysis of small population group trials) <http://www.ideal.rwth-aachen.de/>

⁶ INSPIRE (Innovative methodology for Small Populations Research) <http://www2.warwick.ac.uk/fac/med/research/hscience/stats/currentprojects/inspire/>

⁷ European Parliament News: Clinical trials: clearer rules, better protection for patients, 2 March 2014 <http://www.europarl.europa.eu/news/en/news-room/content/20140331PR41186/html/Clinical-trials-clearer-rules-better-protection-for-patients>

be registered in a central database and a summary of results—positive or negative—must be uploaded within one year after the end of the trial. In addition, researchers must release a full clinical study report containing detailed information about the trial design and analysis, including patient-level data sets, if the medicine is submitted for marketing authorization, irrespective of that application's success. This piece of legislation is expected to come into force mid-2016 after which the EU will fine non-compliant academic researchers and companies. Other aspects of the law include facilitating cross-border cooperation to make clinical trials larger, more viable and more reliable, which should in turn boost efforts to develop treatments for rare diseases. An article published in the *New England Journal of Medicine*, titled 'Access to patient-level trial data – A boon to drug developers'⁸, the authors consider that access to full clinical trial data, including patient data, will achieve the following: increase drug development efficiency and improve cost-effectiveness; improve comparative-effectiveness analysis; and reduce effort duplication among trial sponsors. The authors believe that concerns related to the risk of clinical trial misinterpretation may be misplaced since *“inappropriate secondary data analyses are likely to occur regardless of the nature of the data (and) call for a two-way transparency principle by which any secondary analysis is also to be published and subject to critical review”*.

1.9. Sponsors to post clinical trial summary results in the European Clinical Trials Database⁹

The EMA has announced that sponsors must begin posting clinical trial results in the European Clinical Trials Database¹⁰ (EudraCT) from 21st July 2014, once the final version of EudraCT is launched. Following the recent announcement¹¹ of the new clinical trials regulation No 536/2014/12, and in accordance with the European Commission's Guideline¹³, Clinical Trials Directive 2001/20/EC¹⁴ and Paediatric Regulation¹⁵ to standardize clinical trials throughout the EU, sponsors will be legally required to upload clinical trial results to EudraCT within six or twelve months following trial completion, depending on the trial. Protocols and results information will become increasingly available for the public to access, download and save through the European Union Clinical Trials Register¹⁶. Protocols and

⁸ Eichler H-G, Pétavy F, Pignatti F, Rasi G: Access to Patient-Level Trial Data — A Boon to Drug Developers. *N Engl J Med* 2013; 369: 1577-1579.

⁹ EMA: Posting of clinical trial summary results in European Clinical Trials Database (EudraCT) to become mandatory for sponsors as of 21 July 2014. 19 June 2014

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/06/news_detail_002127.jsp&mid=WC0b01ac058004d5c1

¹⁰ European Clinical Trials Database (EudraCT) <https://eudract.ema.europa.eu/>

¹¹ Publication of the new European Regulation on Clinical Trials, *OrphaNews*, 17 June 2014

<http://www.orpha.net/actor/EuropaNews/2014/140617.html#Edito>

¹² Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *Official Journal of the European Union*, 27 May 2014 <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>

¹³ Commission Guideline — Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006, *Official Journal of the European Union* http://ec.europa.eu/health/files/eudralex/vol-10/2012_302-03/2012_302-03_en.pdf

¹⁴ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, *Official Journal of the European Communities*, 1 May 2001 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>

¹⁵ EMA, Paediatric Regulation

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000068.jsp&mid=WC0b01ac0580025b8b

¹⁶ EU Clinical Trials Register <https://www.clinicaltrialsregister.eu/ctr-search/search>

information from over 23,000 clinical trials registered in EudraCT are already available for public search in the register.

1.10. Application of the EU Regulation on Advanced Therapy Medicinal Products

The European Commission has adopted a Report on the application of the Regulation (EC) No 1394/2007 on Advanced Therapy Medicinal Products (ATMP). In the report, the Commission takes stock of the situation of advanced therapy medicinal products in the EU and has amended the Directive to provide an efficient approach in efforts to further develop ATMPs. The EU has recognized the potential of advanced therapies for a range of populations with unmet needs. To provide for a common framework to market ATMPs, Regulation (EC) No 1394/2007 of the European Parliament and of the Council on ATMP Regulation was adopted in 2007¹⁷. Due to the strenuousness to bring ATMPs to market, a public consultation was issued, the results of which led to the amendment of the Directive 2001/83/EC and Regulation (EC) No 726/2004. The amendments include increased clarification of the scope of the ATMP regulation, avoiding disparities in the classification of ATMPs in the EU. Clarification of the conditions for the application of the hospital exemption, as well as the role of data obtained in the context of marketing authorization procedures is expected. The Directive also calls for the revision of ATMP authorization requirements, with a view to ensuring that conditions are proportionate and adapted to specific ATMP characteristics. The Directive highlights the need to streamline marketing authorization procedures, extend certification processes and clarify the link between certification and marketing authorization practices. The Directive also aims to provide a more favorable environment for ATMP developers working in academic or not-for-profit settings. Early contact with authorities should be promoted through a fee-reduction application for scientific advice and by extending the certification scheme to these developers. The Directive suggests fee-reduction incentives to reduce the financial impact of post-marketing obligations¹⁸.

1.11. Introduction of fee incentives for SME post-authorization activities in Europe^{19,20}

The EMA has announced a 1.5 percent fee increase for applicants and marketing-authorization holders from 1st April 2014 to account for inflation. The agency introduced, simultaneously, new post-authorization fee incentives to support micro-, small- and medium-sized enterprises (SMEs). SMEs have been at the forefront of developing innovative medicines and developed over 60 percent of orphan medicinal products (OMPs) between

¹⁷ Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, 10 December 2007 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:324:0121:0137:en:PDF>

¹⁸ Report from the Commission to the European Parliament and the Council in accordance with Article 25 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, 28 March 2014 http://ec.europa.eu/health/files/advtherapies/2014_atmp/atmp_en.pdf

¹⁹ EMA, Fee reductions for designated orphan medicinal products, 19 November 2013 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2011/02/WC500102327.pdf

²⁰ EMA news release: European Medicines Agency introduces new fee incentives for SMEs for post-authorisation activities, 1 April 2014 http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/04/news_detail_002058.jsp&mid=WC0b01ac058004d5c1

2010 and 2012. The EMA's incentives benefit patients suffering from rare diseases as they lower costs for cash-strapped SMEs and speed up market entry of new OMPs. SMEs that had previously raised concerns about fee increases^{21,22} should be reassured by the EMA's announcement. The incentives include a 100 percent fee reduction for micro-sized companies and a 40 percent reduction for small- and medium-sized enterprises. Other types of support the EMA provides for SMEs include fee reductions for scientific advice throughout the medicine's lifecycle, outreach programs and dedicated newsletters.

1.12. Publication of the new European Regulation on Clinical Trials²³

Following months of negotiation and revisions of the European Commission's Proposal for a Regulation on clinical trials, and the repeal of Directive 2001/20/EC²⁴, the much anticipated new European Regulation on Clinical Trials was finally published in the Official Journal of the European Union²⁵ on 27th May 2014. The European Council and Parliament reached an agreement in December 2013 before the Regulation was formally adopted last April. Under the new Regulation, multinational clinical trials will be easier to conduct. The new rules will facilitate cross-border collaboration for larger clinical trials, essential for research on rare diseases. For years, patients, researchers and the industry have expressed dissatisfaction with the restrictive rules of former Clinical Trials Directive 2001/20/EC²⁶. Administrative burden, regulatory requirements and increasing fees have resulted in a marked 25 percent decline in clinical trial numbers conducted in Europe over the past several years. Under the new Regulation, applicants throughout the EU are required to submit a set of uniform documents for clinical trial authorization. Applications will be processed via a single clinical trial approval system to ensure a single outcome per country, thus avoiding multiple applications for trials in different member states, and reducing fees and time for application approval. The European Commission estimates that the new rules could save researchers up to 800 million Euros a year.

The new regulatory requirements will be adapted according to the level of risk patients are exposed to during a trial. The Regulation thereby introduces the concept of 'low-intervention clinical trial', for instance for studies comparing already authorized medicines. Another major objective of the Regulation is to increase transparency. All results, positive

²¹ The European Association for Bioindustries (EuropaBio), European Biopharmaceutical Enterprises (EBE) Fee reduction for Orphan Medicinal Products – your letter of 12 December 2012, reference EMA/663512/2012, 2 April 2014 http://www.orpha.net/actor/EuropaNews/2013/doc/Letter-incentives-EBE_EuropaBio.pdf

²² EMA, Fee reductions for orphan medicinal products (response letter to EuropaBio and EBE), 13 May 2013 <http://www.orpha.net/actor/EuropaNews/2013/doc/Letter-to-EuropaBio-EBE---reply-to-letter-02APR13.pdf>

²³ EMA Press release: European Medicines Agency welcomes publication of the Clinical Trials Regulation, 28 May 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/05/WC500167798.pdf

²⁴ Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, 17 July 2012 http://ec.europa.eu/health/files/clinicaltrials/2012_07/proposal/2012_07_proposal_en.pdf

²⁵ Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, *Official Journal of the European Union*, 27 May 2014 <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32014R0536&from=EN>

²⁶ Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, *Official Journal of the European Communities*, 1 May 2001 <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>

and negative, will have to be published in a publicly-accessible database, reflecting demands from initiatives such as AllTrials. *OrphaNews* kept a close watch on EMA's Work Programme 2014²⁷ for data sharing and transparency²⁸ via a publicly-accessible database throughout April this year. Finally, while individual countries will continue to constitute their own Ethics Committees for the assessment of clinical trials, the Commission reserves the right to monitor EU and non-EU countries in order to ensure rules are uniformly enforced and compliant with EU requirements in the case of trials conducted outside Europe. The new Regulation will come into effect in mid-2016 at the earliest. For the rare disease community, the Regulation's support for rapid and in-depth application assessment for clinical trials on orphan drugs is encouraging. Expected benefits of the new regulation will therefore have to be patiently awaited. But many hope that the new Regulation will translate into increased numbers of clinical trials across Europe, for both common and rare diseases.

On 12th June, shortly after the EMA published these new regulations, the agency announced it would modify data sharing rules²⁹. The announcement came following pressure from European ombudsman Emily O'Reilly, AllTrials Campaign in an open letter³⁰ to EMA director Guido Rasi, the European Consumers Organisation (BEUC), the European Association of Hospital Pharmacists and GIMBE. The EMA will allow researchers to download, save and print clinical trial data for non-commercial use, a development on the previous proposed draft which limited researchers to on-screen data consultation only. While researchers welcome this draft amendment, they and Ms. O'Reilly remain concerned about the terms of use and redaction policies which would give clinical trial sponsors control over the data they publish. The new rules are expected to be effective from 1st October 2014.

1.13. EMA's Work Programme 2014 shows great potential for developers of orphan medicinal products and the rare disease community

The Agency has identified key objectives in the area of evaluating activities for human medicines 2014, all of which should help bring more orphan medicinal products to the market. The Agency will aim to increase the success rate for marketing-authorization applications through a more active use of scientific advice and other pre-application support to encourage the development of new medicines, particularly orphan medicinal products. The Agency will also work towards facilitating the use and development of emerging technologies and approaches in developing new medicinal products in addition to improving international cooperation in pre-authorization support, especially in the area of scientific advice. This was also reflected in the Agency's workshop on worldwide orphan medicinal designation. Broadly, the Agency aims to offer support for innovative methodologies, such as

²⁷ EMA Work Programme 2014, 12 December 2013

http://www.ema.europa.eu/docs/en_GB/document_library/Work_programme/2014/03/WC500163394.pdf

²⁸ So D, Joly Y, Knoppers BM: Clinical trial transparency and orphan drug development: recent trends in data sharing by the pharmaceutical industry. *Public Health Genomics* 2013; 16(6): 322-35.

²⁹ EMA agrees policy on publication of clinical trial data with more user-friendly amendments, 12 June 2014

http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/06/WC500168342.pdf

³⁰ Goldacre B, Godlee F, Heneghan C, Tovey D, Lehman R, Chalmers I, Lind J, Barbour V, Brown T: Open letter: European Medicines Agency should remove barriers to access clinical trial data. *BMJ* 2014; 348: g3768 <http://www.bmj.com/content/bmj/348/bmj.g3768.full.pdf>

biomarker qualification, as well as for the development of new approaches and medicines, such as stem-cell technology. In addition to providing advice to sponsors applying for orphan medicines, pediatric medicines, advanced therapies, the Agency also envisions providing greater support to the HTA throughout the “*lifecycle of the medicinal product*”. The Agency will also work further towards facilitating early stages of medicines development, implementing clinical trials legislation, enhancing cooperation within the European medicines network and with other European and international partners with increased transparency as a key focus. These goals and objectives outlined in the EMA Work Programme 2014 will prove to be greatly beneficial in faster patient access to OMPs.

1.14. Launch of three major -OMICS projects in the field of RD

The EC announced its commitment to support the logistical organization of IRDiRC activities through a dedicated support action topic in the FP7-HEALTH-2012-INNOVATION-1 call for proposals (Work Programme 2012). The project funded in this topic, SUPPORT-IRDiRC (www.support-irdirc.eu) provides a Scientific Secretariat for the IRDiRC since its launch in October 2012 for a six-year period. The Call FP7-HEALTH-2012-INNOVATION-1 resulted in the funding of a number of projects contributing directly to the IRDiRC objectives for a total of 40 million Euros. Three large-scale integrating projects are being funded in the area of -Omics for rare diseases: EUReOmics (www.eurenomics.eu) will systematically apply -omics technologies for the molecular characterization of rare kidney disorders in view of developing new diagnostics and treatments, NEUROMICS (rd-neuromics.eu) aims to use the most sophisticated -omics technologies to revolutionize diagnostics and develop pathomechanism-based treatments for large groups of rare neuromuscular and neurodegenerative diseases and RD-Connect (rd-connect.eu) will create an integrated platform connecting registries, biobanks and clinical bioinformatics for rare disease research into a central resource for researchers worldwide. Ten new research projects were funded for preclinical and clinical development of orphan drugs with the major involvement of industry and small- and medium-sized enterprises. The kick-off meetings of these projects were held in Barcelona on 25-27 January 2013.

With today’s progress in gathering rare disease information into patient registries, biobanks and other clinical databases comes the challenge of connecting these data sources to conduct rational genetic, diagnostic and therapeutic research. In an article published in the *Journal of General Internal Medicine*³¹, Thompson *et al.* describe the role of RD-Connect as an EU-funded platform to integrate and cross-link data sources in a comprehensive yet secure mode. Since its launch in January 2013, in association with partner projects Neuromics, EUReOMICS and SUPPORT-IRDiRC, RD-Connect has begun identifying rare disease biobanks, developing tools to merge and search data, and developing regulatory and ethical standards to optimize data sharing and ensure patient confidentiality. By drawing on

³¹ Thompson R *et al.*: RD-Connect: An Integrated Platform Connecting Databases, Registries, Biobanks and Clinical Bioinformatics for Rare Disease Research. *Journal of General Internal Medicine* 2014; 29 Suppl 3: S780-7.

and incorporating resources from twenty-seven associated institutions, RD-Connect will contribute towards IRDiRC's goals to develop diagnostic tools and new therapies for rare diseases.

2. Recent initiatives taken to speed up R&D in the USA

2.1. Initiatives in the USA to increase the dialogue with the public to help patients and Industry to better understand the therapy development process for rare diseases.

The FDA's Office of Orphan Products Development (OOPD), in collaboration with the Center for Drug Evaluation and Research (CDER), announced the launch of web-based educational resources for patients and industry³² on FDA-related rare disease topics, the first of which was revealed on Rare Disease Day, 28 February, 2014 (www.rarediseaseday.org). The resources covered on the website elucidate mechanisms to interact with the agency and access therapies that are currently being studied. They have also released an FDA Voice Blog focusing on initiatives related to pediatric rare diseases. This is part of FDA's ongoing efforts to bring effective treatments for rare disease patients, which have, until now, been commendable. FDA has reiterated the importance of listening to patient comments and concerns and interacting with them in order to address their needs and better serve them³³.

2.2. US initiative regarding use of foreign data in support of new orphan drug applications for approval by the FDA³⁴

The globalization of clinical research is demonstrated by the exponential increase in clinical trials conducted outside the United States. These have been submitted to the US Food and Drug Administration (FDA) for marketing approval of new drug applications. An article published in *Nature* written by FDA employees, discusses their experience with results submissions from clinical trials performed outside the US in specific therapeutic areas, including orphan drugs. They also discuss the *"extent of this practice, differences between the effectiveness and safety outcomes of studies conducted inside and outside the United States, and the FDA's approach to acceptance of these trials"*. According to the authors, in the area of orphan drugs, the FDA exercises *"greater regulatory flexibility"* due to the rarity of the diseases in question and the difficulty of finding adequate number of patients to perform an efficient clinical trial, thus making FDA approval for orphan drugs based entirely on foreign data more likely. The authors provide a several examples where the FDA has approved drugs based completely on data gathered from countries other than US. These examples include the approval of velaglucerase alfa for type 1 Gaucher disease for which the clinical trials were conducted in five countries - Argentina, Paraguay, Israel, Russia, and Tunisia. The FDA has also approved carglumic acid for the treatment of hyperammonemia in

³² FDA, Educational Resources for Patients, Advocacy Groups, Research Investigators and Orphan Product Developers <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/ucm385535.htm>

³³ FDA Speeds Innovation in Rare Disease Therapies <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm387513.htm>

³⁴ Khin NA: Regulatory and scientific issues regarding use of foreign data in support of new drug applications in the United States: an FDA perspective. *Clinical Pharmacology & Therapeutics* 2013; 94(2): 230-42.

patients with N-acetyl-glutamate synthase deficiency of the urea cycle was also based on data from France, Germany, and the United Kingdom. Thus, the authors confirm the FDA's eagerness on the use of cross border data from clinical trials for orphan drugs.

2.3. PCORI of the United States announces expert panel on rare disease³⁵

The Patient-Centered Outcomes Research Institute (PCORI, www.pcori.org) was authorized by the US Congress to conduct research to provide information about the best available evidence to help patients and their health care providers make more informed decisions. PCORI approved thirteen new members for its Advisory Panel on Rare Diseases. The panelists will apply their experience and expertise to advise PCORI on its research priorities in the area of rare disease and engage with the rare disease research community. The thirteen new panelists represent a range of stakeholder groups and perspectives, including people with rare diseases, family caregivers, clinicians, drug and device makers, and researchers, among others. Over a third of panelists will represent patients and patient advocates. The panel will assist PCORI in identifying experts to serve on *ad hoc* advisory panels, as needed, to consider research issues related to particular rare diseases and to advise the US Congress.

2.4. NIH inventions translate into drugs and biologics with high public impact

The role of National Institute of Health (NIH) in leading translational success of drugs is not widely known. After 1980, two legislations passed in the United States, the Bayh-Dole Act and the Stevenson-Wydler technology Innovation Act, allowed and incentivized technology transfer from government funded institutions to the private sector for commercialization. Whether these legislative changes have helped secure more drug entries into the market is a point of contention. Public-sector research institutions (PSRIs) have been demonstrated to have a greater immediate effect on improving public health than previously believed, as they have contributed significantly towards drug development³⁶. A study shows that the NIH-Intramural Research Program (IRP) has had a disproportionately high level of impact on bringing drugs to the market through the US Food and Drug Administration (FDA). An in-depth comparison of the specific contributions of the NIH-IRP and other PSRIs to the development of drugs and biologics approved by the FDA was published in *Nature Biotechnology*³⁷. The authors, who belong to the Office of Technology Transfer at NIH, have procured data which reveals that NIH-IRP inventions have had a disproportionately greater impact as the largest institutional contributor to the PSRI drugs. Among other categories, NIH-IRP has had a great impact on the number of drugs granted orphan status and drugs developed under New Drug Applications (NDAs), because they offer major treatment benefits.

³⁵ PCORI Announces Expert Panel on Rare Disease, 25 March 2014 <http://www.pcori.org/blog/pcori-announces-expert-panel-rare-disease>

³⁶ Stevens AJ *et al.*: The Role of Public-Sector Research in the Discovery of Drugs and Vaccines. *The New England Journal of Medicine* 2011; 364; 6.

³⁷ Chatterjee SK, Rohrbaugh ML: NIH inventions translate into drugs and biologics with high public health impact. *Nature Biotechnology* 2014; 32(1): 52-8.

Of all the FDA-approved drugs, 153 drugs materialized from inventions in extramural PSRIs or NIH-IRP, out of which 14.4 percent of drugs received licenses from NIH-IRP alone. The authors revealed that the NIH-IRP contributions to obtaining market authorizations are disproportionately large relative to its level of funding (11.2 percent of all NIH research funds). While NIH-IRP has made higher contributions to some therapeutic categories than to others, they have significantly overshadowed extramural PSRIs by contributing towards FDA approved drugs. Notably, 15 percent of the 39 PSRI drugs that received orphan status used licensed technology from the NIH-IRP. Furthermore, while the funding for NIH-IRP in 2010 was around US\$3.3 billion, the global net sales of drugs and biologics from NIH-IRP inventions amounted to at least US\$6.9 billion. The percentage of large companies executing NIH-IRP invention licenses exceeds small companies or start-ups. This differs from other PSRIs where smaller companies and start-ups have played a larger role. This is possibly because NIH-IRP cannot actively participate in the establishment of a company around the institution's inventions, while other PSRIs can and thus be more involved with startup or spinoff companies. The success of the NIH-IRP technology transfer program may be related to its resources and structures where scientists have access to high-quality resources and the opportunity to address biomedical challenges in a relatively stable funding environment. Furthermore, the authors also highlight the high-quality technology transfer infrastructure at the NIH, making license transmission smooth and quick.

2.5. Discovering New Therapeutic Uses for Existing Molecules³⁸

This NIH-funded project is a collaborative project designed to develop partnerships between pharmaceutical companies and the biomedical research community to identify new therapeutic uses for existing compounds for rare and common diseases that have already entered the marketplace or have previously been involved in clinical trials. NIH has awarded nine grants to evaluate new therapeutic uses for eight drugs made available by pharmaceutical firms. Around 58 compounds have already been provided by several pharmaceutical companies covering eight disease areas, including Alzheimer's, calcific aortic valve stenosis, Duchenne muscular dystrophy, lymphangiomyomatosis, peripheral artery diseases, smoking cessation and schizophrenia.

2.6. Fostering orphan medicine research and development: The success of the FDA's Orphan Products Grants Program³⁹

With support from the FDA's Office of Orphan Products Development, the authors of an article published in *Expert Opinion on Orphan Drugs* studied the impact of the FDA's Orphan Products Grants Program on the development of medicines and products for rare diseases. Since the Orphan Drug Act launch in 1983, US\$320 million have been awarded to clinical studies on rare disease products. From an initial US\$500,000 in 1983, funding has continued

³⁸ NIH, Discovering New Therapeutic Uses for Existing Molecules <http://www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html>

³⁹ Imoisili MA, Mueller C, Miller Needleman CI: Fueling the development of products for rare diseases: the impact of the FDA's orphan products grants program. *Expert Opinion on Orphan Drugs* 2014; 2(8): 807-815.

to rise, reaching US\$12 million in 2013, a slight decrease from the US\$14 to US\$15 million allocated annually from 2005 to 2012. The grant program receives on average 90 to 100 applications a year. Though Imosili *et al.* note that applicants are US-based essentially, foreign public and private entities are also eligible to apply under an active Investigational New Drug application (IND) or Investigational Device Exemption (IDE). In fact, the program funds a number of grants concerning multiple international sites. Based on scientific and technical criteria, applications are reviewed and evaluated by an independent panel of experts. This independent review process avoids funding projects that are not regulatory sound or likely to meet market approval. Out of 567 awarded grants, the program's funds have contributed to the authorization of thirty-four drugs, nine biologics and eight devices, representing around 10 percent of orphan products. Imosili *et al.* highlight that incentives such as the FDA's grant program are effective to foster research on rare diseases. Grants provide a significant source of funding for investigators with limited resources. While FDA's Orphan Products Grants Program is one of the main program to fund rare disease clinical trials, others such as NIH's Therapeutics for Rare and Neglected Diseases (TRND) program and IRDiRC aim to accelerate the development of drugs and diagnostic tools for rare diseases.

2.7. The FDA issues a strategic plan to accelerate the development of therapies for children with rare diseases⁴⁰

In response to growing clinical, technical and economic challenges to bring to market drugs and diagnostic products for pediatric rare disease (PRD) patients, the FDA conducted a public workshop in January 2014 to discuss issues with academics, researchers, patients, advocacy groups, industry and regulators. Based on their contributions, the FDA published a strategic plan last July, *Accelerating the Development of Therapies for Pediatric Rare Diseases*, proposing four objectives to improve children's access to orphan drugs and devices.

The **first objective** is to improve basic and translational science on pediatric rare diseases. Regulators call for a better understanding of rare disease natural history, *i.e.* disease evolution if left untreated. Progression of rare diseases is often poorly understood due to small numbers of cases. Knowledge gaps are particularly marked in pediatric groups, in which diseases evolve in an age-dependent mode. The FDA proposes applying modeling techniques to predict orphan product performance in different age and patient groups.

The **second objective** is to initiate and reinforce interaction, partnerships and collaboration between stakeholders (researchers, industry, regulators, patients, advocates and physicians). Inter- and intra-regulatory agency communication contributes towards harmonizing standards for rare disease classification and therapeutic development. The FDA and the EMA, for instance, hold regular discussions to coordinate international research and

⁴⁰ FDA Report: Complex Issues in Developing Drugs and Biological Products for Rare Diseases and Accelerating the Development of Therapies for Pediatric Rare Diseases Including Strategic Plan: Accelerating the Development of Therapies for Pediatric Rare Diseases, July 2014.

clinical protocols. The FDA recommends strengthening international collaborations to pool resources and accelerate product development plans for rare diseases.

The **third objective** is to further develop standards and methods to monitor the safety and efficacy of orphan products. This is particularly relevant to long term treatments for patients with chronic rare diseases. The FDA recommends guidance documents and investigator training to improve product development efficiency and age-specific product safety, suitability and effectiveness under the Best Pharmaceuticals for Children's Act (BPCA) of 2002 and the Pediatric Research Equity Act (PREA) of 2003. Dose-dependent safety assessments are essential to treat pediatric rare disease patients effectively. The FDA recommends using biomarkers, for instance, to help find appropriate doses and measure dose responses.

The **fourth objective** is to enrich the FDA's PRD evaluation process by involving patients, patient advocates and caregivers in clinical trial designs early on. Criteria such as patient benefit-risk preferences, clinical outcome measures and feedback on quality of life should constitute part of the drug assessment process more systematically and appropriately. The FDA recommends greater flexibility and adaptability in orphan product evaluation processes, building on existing evidence, to overcome the limiting effect of small patient numbers in rare disease clinical trials. This objective builds on the agency's Rare Pediatric Disease Priority Review Voucher (PRV) program of 2012, to further accelerate the development of pediatric orphan products.

While orphan medicinal product development is challenging at the best of times, developing orphan products for children with rare diseases is all the more complex due to age-related factors and ethical considerations. Information and clinical evidence on medical product safety and efficacy in children with rare diseases is generally inadequate as a result of small patient numbers, age-specific physiology and responses to treatment. The FDA's recommendations to increase collaboration and transparency aim to draw attention to the need for additional and improved pediatric rare disease care.

3. Recent initiatives to speed up research in Asia

3.1. Launch of the Chinese Rare Disease Research Consortium (CRDRC)⁴¹

The Chinese Rare Disease Research Consortium (CRDRC) was formally announced on 14 September 2013. Over twenty universities, colleges and institutes and fifty specialists are now members of this consortium. CRDRC aims to team up with several other researchers and organizations investing in rare disease research in China. The goals of CRDRC are multifold as they include establishing a national registry for rare diseases in China⁴² as well

⁴¹ China celebrates the founding of the Chinese Rare Disease Research Consortium, *OrphaNews* 29 October 2013.

⁴² Song P *et al.*: China's first rare disease registry is under development. *Lancet* 2011; 378(9793): 769-70.

as establishing and providing access to harmonized data and samples. Efforts of CRDRC will go towards identifying five to thirty rare disease genes per year and make genetic testing based on these genes available for patients. The CRDRC also aims to perform translational research with newly identified genes and facilitate development of therapeutic strategies. CRDRC will endeavor to provide funding support for rare disease research in China by forming an alliance with the China Natural Science Foundation, the Ministry of Science and Technology, and the Ministry of Health. These will include participating in joint calls or international collaborative funding for rare disease research with the EU, Australia, and other countries. Finally CRDRC will seek to launch a Rare Disease Research Institute in China to centralize the rare disease research efforts in China.

3.2. Launch of the first web-based Korean Rare Disease Knowledge Base (KRDK)⁴³

The Korean Rare Disease Knowledge Base (KRDK, www.snubi.org/software/raredisease) was established in 2013. It includes disease summaries and reviews (520 disease summaries and 48 disease reviews), a causal gene list and a directory of laboratories and clinics. The database intends to add an orphan drug database to its repertoire. Modeled on the genetic database GeneTests (www.genetests.org), this database provides quick querying and prevents the appearance of redundant data. The database uses Orphanet as the main resource for information on rare diseases, genetic data and reviews. The database provides a summary of the patient registry - Bio Electronic Medical Record (BioEMR) and is linked to the Genome Research Information Pipeline to provide all information relating to genes.

3.3. Japan reforms its policy for intractable diseases⁴⁴

The Committee for the Rare and Intractable Diseases in Japan proposed a reform of the current policies on intractable diseases to the Commission for Specific Disease Control under the Health Science Council. The proposal was accepted on 31 January 2013. The objective of the proposal was to reform the current policies on intractable diseases by improving the quality of the development of effective treatment methods, introducing a fair and stable medical expense subsidy system, and enhancing awareness among the public. To accomplish these objectives, the Committee recommends increasing the number of reimbursed intractable disease treatments from 56 to 300, and to provide a comprehensive long-term care and social support for patients with intractable diseases. To ensure fairness, the Committee recommends narrowing the subsidy beneficiaries only to patients facing a severe disruption to lifestyle. The Committee also placed great importance to strengthening research and promoting comprehensive and strategic study of intractable diseases. Japanese legislation encourages research on rare diseases and development of orphan drugs. It has also brought changes to the pricing and reimbursement systems. It facilitates access to

⁴³ Seo H, Kim D, Chae JH, Kang HG, Lim BC, Cheong HI, Kim JH: Development of Korean rare disease knowledge base. *Healthcare Informatics Research* 2012; 18(4): 272-8.

⁴⁴ Japan reforms policy on rare disease subsidies, *OrphaNews*, 20 February 2013.

orphan drugs, specific research programs to promote research and development, and a government-supported information center to promote rare disease understanding⁴⁵.

⁴⁵ Song P *et al.*: Rare diseases and orphan drugs in Japan: developing multiple strategies of regulation and research. *Expert Opinion on Orphan Drugs* 2013; 1(9): 681-83.

II. RECENT INITIATIVES TO FACILITATE TRANSNATIONAL COLLABORATIONS

1 Recent international initiatives

1.1. Initiative to develop further international cooperation between regulators in the field of orphan medicinal products

The EMA and FDA further developed their collaborative efforts in late February 2010 with the introduction of an agreement that permits a single annual report to be submitted for orphan products designated in both the EU and the US. Prior to this, sponsors with designations in both places were required to submit two separate reports detailing the progress of drug development, including *“a review and status of ongoing clinical studies, difficulties in testing, and any potential changes that may impact the product’s designation as an orphan product”*. Each regulatory body will continue to conduct its own assessment of the reports, to appraise whether information satisfies the legal and scientific requirements of each agency. The option of submitting a single annual report to both agencies benefits sponsors by reducing the duplication of efforts. The new measure, unveiled on the occasion of Rare Disease Day 2010, is one of several streamlined initiatives the two agencies have undertaken in recent years as part of a transatlantic agreement designed to enhance cooperation between the two agencies.

Other initiatives include a pilot program, launched in August 2010, on joint good manufacturing practice (GMP) inspections for manufacturers of medicinal products and a three-year pilot announced for April 2011. This will allow simultaneous evaluation of 'quality by design' aspects of applications submitted to the Agency and to the FDA. Quality by design is an enhanced systematic and science-based approach to the development and manufacture of medicines that ensures better quality of medicines⁴⁶. In 2011 the FDA and EMA hosted the first joint workshop on applications for orphan designation, marking the first occasion in which sponsors have been able to discuss in real time applications for designation with both Regulatory Authorities. The FDA published a report of their activity in the realm of innovative medicines in 2011. Orphan medicinal products come out well, making up almost a third of the 35 innovative medicinal products that were approved by the FDA in fiscal year 2011. Moreover, the FDA approved nearly half (16) of the innovative drugs under the agency’s priority review program. This scheme accelerates the approval process for drugs that may offer major advances in treatment. The FDA defines innovative medicines as ‘new molecular entities’, novel chemical structures, including biological products, which have never been approved before to treat any disease, and often represent the most innovative drugs entering the market. Ten of the innovative products approved in fiscal year 2011 have orphan indications. The parallel submission process helps rationalize the development of orphan medicines by facilitating access to parallel scientific advice (protocol

⁴⁶ EUCERD Report: 2012 Report on the State of the Art of Rare Diseases Activities in Europe – Part II: Key developments in the field of rare diseases in Europe in 2011, July 2012.

assistance) from the two regulatory authorities. Based on the success of this collaboration, in 2012, 62 percent of applications were submitted in parallel in the EU and the US. The EMA also began to collaborate with the Japanese regulatory authorities. An increase in the number of Japanese orphan drug designations with prior European designations was observed in 2012. A dialogue with Health Canada has been established⁴⁷.

A workshop on orphan product designation and grants took place on 10 March 2014 at the EMA⁴⁸. Organized by the EMA, the FDA and for the first time the Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), this one day workshop was an effort towards accelerating treatment development for rare disease patients. The agencies representing the three areas, with contributions from Canada and Australia, have worked jointly over the years to improve the quality and number of orphan designations and encourage parallel submission for orphan medicinal designation. The workshop aimed to enhance efficiency and avoid ambiguity between the agencies and sponsors by highlighting three areas, the process of granting orphan medicine designation by the FDA, MHLW/PMDA and EMA, post-designation incentive programs and grants available through the FDA, European Commission and NIBIO (Japan) intended to boost research and development for rare diseases⁴⁹.

1.2. Initiative to tackle the specificities of the health technology assessment process for orphan medicinal products⁵⁰

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR, www.ispor.org) not-for-profit organization implemented a rare disease Special Interest Group (SIG) in 2014⁵¹. ISPOR promotes worldwide pharmacoeconomics and outcomes research and facilitates the translation of this research into useful information for healthcare decision makers to increase efficiency, effectiveness and access to healthcare. In the face of increasing rare disease diagnostics and treatments, ISPOR's Rare Disease Special Interest Group aims to elucidate health technology assessment (HTA) issues concerning orphan medicinal products, in efforts to help researchers, payers, patients and the industry overcome challenges to develop and assess new or existing diagnostics and therapeutics. Four working groups represent the four goals of the Rare Disease SIG:

- ▶ Rare Disease Terminology & Definitions Used in Outcomes Research Working Group
- ▶ Challenges in Assessing and Appraising Rare Disease Treatments Working Group

⁴⁷ EUCERD Report: 2013 Report on the State of the Art of Rare Diseases Activities in Europe – Part II: Key developments in the field of rare diseases in Europe in 2012, July 2013.

⁴⁸ EMA, Joint European Medicines Agency (EMA), US Food and Drug Administration (FDA), and Japanese Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA) orphan medicinal product workshop, 10 March 2014 http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/03/WC500164157.pdf

⁴⁹ EUCERD Report: 2014 Report on the State of the Art of Rare Diseases Activities in Europe – Part II: Key developments in the field of rare diseases in Europe in 2013, July 2014.

⁵⁰ ISPOR (International Society for Pharmacoeconomics and Outcomes Research) is implementing a rare disease Special Interest Group (SIG), *OrphaNews*, 15 October 2014.

⁵¹ ISPOR Rare Disease Special Interest Group: challenges in assessment and appraisal of rare disease diagnostics & treatments working group <http://www.ispor.org/sigs/RareDisease/ChallengesAssessingAppraisingDT.asp>

- ▶ HTA of Rare Disease Diagnostics and Treatments Working Group
- ▶ Methodology - Measuring Use, Costs and Effectiveness of Rare Disease Care Working Group.

1.3. Launch of a Global Alliance to aid genomic data sharing⁵²

The cost of genome sequencing has fallen a million fold and is becoming increasingly affordable and accessible. While advances in genome sequencing have provided a wealth of knowledge, data collected and studied are mostly disorganized and dispersed. Experts highlight that no agreed-upon standards exist to represent genetic data or data sharing. Additionally, no common procedures currently exist to ensure that patients consent to sharing their information. To better serve the patient, research and clinical communities, fifty representatives from eight countries met earlier in 2013 to discuss how they could work collaboratively towards optimal use of generated data. The Global Alliance was created to develop standards and policies to encourage data-sharing. The Alliance hopes to tackle other ethical issues that have cropped up following the genomics revolution. Such privacy and informed-consent concerns may prevent researchers from sharing data through cloud-computing platforms and analysis tools. The Global Alliance plans to base its model on the World Wide Web Consortium, which established HTML standards leading to an unprecedented growth of web pages across the Internet and also the Human Genome Project for its rapid development. The consortium consists of over seventy institutions in thirteen countries and counts IRDiRC as one of its members.

1.4. Publication of a bio-entrepreneurs guide for orphan drug developers

An article published in 2014 in *Nature Biotechnology*⁵³ analyzes how regulatory incentives on orphan drugs have helped bio-entrepreneurs, with an orphan drug focus, reap financial rewards based on the likelihood of investment from big pharmaceuticals. The authors identified “*the important acquirers, average price of purchase and at what stage orphan disease companies get bought*”, which they believe should “*inform bio-entrepreneurs about the orphan drug space and their potential futures in it*”. The authors identified ninety-eight mergers and acquisitions using the HBM Partners Mergers and Acquisitions Report⁵⁴ and analyzed the conditions under which companies with an orphan focus are acquired. The authors discovered that, on average, companies with and without an orphan designation (ODN) on their lead compound were bought within eight years of their founding. However, companies with an ODN compound were bought at phase II of drug trials, while companies without an orphan focus were bought during phase III trials. The authors suggest this may be due to the perceived (and accepted) market risk of orphan drugs or because of the reluctance of bio-entrepreneurs with an orphan focus to sell their company after phase II trials. Additionally, the authors discovered that from “*(a) financial standpoint it is about as*

⁵² History of the Global Alliance for Genomics & Health <http://genomicsandhealth.org/about-global-alliance/history>

⁵³ Rooswinkel R, Mulder GJ, van Deventer S: Acquiring orphans. *Nature Biotechnology* 2014; 32:213–216.

⁵⁴ HBM Partners: HBM Pharma/Biotech M&A Report 2012. January 2013 <http://www.hbmpartners.com/wAssets/docs/industry-reports/HBM-Pharma-Biotech-M-A-Report-2012.pdf>

attractive to develop drugs for a rare disease as it is for a more common illness". Keeping this data in mind, the authors advise bio-entrepreneurs with an orphan-focused company that their *"financing status should allow for the complete development of a compound in-house"*. The authors also provide statistics on big pharma acquisitions and development of orphan products. They report that during 2008-2012, Pfizer was the biggest acquirer, followed by Gilead, Roche and Shire. While Novartis, GlaxoSmithKline and Roche did not acquire any companies, they did develop a number of ODNs during this period. Thus the authors warn that *"although most pharmaceutical companies have in-house ODN programs, only a subset of big pharma is interested in acquiring orphan-designated drugs"*. The authors recognize the challenges bio-entrepreneurs face while starting a company with an orphan focus and believe that this analysis should provide them with indications on how to optimize their investment.

1.5. Launch in 2013 of the first seed fund dedicated to innovative biotherapies and rare diseases in France: a joint action of the AFM-Téléthon and of the Fonds National d'Amorçage⁵⁵

It is against this background that the AFM-Téléthon (which has been developing a variety of innovative therapeutic approaches over the past 25 years) and the Fonds National d'Amorçage (FNA) (which provides funds towards innovative biotherapies and rare diseases) have joined forces to constitute the first seed fund dedicated to innovative biotherapies and rare diseases. This action forms part of an *"Environmental, Social and Governance"* process. With an initial endowment of 50 million Euros, for a final target of 120 million Euros, the fund aims to create a portfolio of 12 to 15 participants in companies at the seed stage. The amount invested will be between 3 and 10 million Euros per company. The AFM-Téléthon has contributed to a budget of 30 million Euros, and CDC Entreprise, via the FNA, has bestowed 20 million Euros. The fund will target innovative SMEs with strong development potential that have been in existence for less than eight years. They must also follow standards that are consistent with the industrial development of therapies such as gene therapy, cell therapy, pharmacological modulation of gene expression, monoclonal antibodies, therapeutic proteins and immunotherapies.

1.6. Initiative to measure the value of biobanks and databases⁵⁶

Sharing resources such as biobanks and databases is an essential part of biomedical research as it enhances knowledge production⁵⁷. Due to this there is a rising requirement *"to improve access complemented with efforts of end-users to recognize and acknowledge these resources"*. In order to develop a set of tools that will help efficient sharing and determine the impact of biobanks and databases, the Bioresource Research Impact Factor (BRIF, www.bioshare.eu/content/bioresource-impact-factor) indicator was created. The BRIF work

⁵⁵ Groupe Caisse des Dépôts: AFM-Téléthon and FNA launch the 1st seed-stage fund dedicated to innovative biotherapies and to rare diseases. 22 May 2013 <http://www.caissedesdepots.fr/en/news/all-the-news>

⁵⁶ IRDiRC: The BRIF initiative: a tool to facilitate bioresource sharing <http://www.irdirc.org/?p=2297>

⁵⁷ DeCastro P *et al.*: Open Data Sharing in the Context of Bioresources. *Acta Informa Medica* 2013; 21(4): 291-292.

has been divided into subgroups: BRIF identifiers, BRIF parameters, BRIF in access and sharing policies, BRIF dissemination and BRIF and journal editors. The different BRIF subgroups aim to expand bioresource content sharing and circulation through the development of specific tools and standards to sit bioresources in journals⁵⁸. One objective of BRIF is to make groups conscious of *“specific issues related to bioresources, creating awareness on the BRIF project and, possibly, proceed to amend editorial guidelines by including reference to bioresources”*. So far, actions have been directed to the International Committee of Medical Journal Editors (ICMJE www.icmje.org), the Committee on Publication Ethics (COPE publicationethics.org) and the European Association of Science Editors (EASE www.ease.org.uk). The ICMJE recommended connecting with the EQUATOR network (www.equator-network.org), a repository of reporting guidelines, while COPE agreed to discuss a declaration of openness for promoting specific guidelines. Additionally, EASE Council members agreed on including the subgroup proposed in the updated version of the Guidelines⁵⁹ to encourage citation of the bioresources with their name or identifier.

1.7. YODA has a possible answer to open access for sharing clinical trial data⁶⁰

The recently developed Yale University Open Data Access Project⁶¹ (YODA) provides a methodology to patients and physicians for rigorous and objective evaluation of clinical trial data. According to YODA, the project *“ensures all necessary information about a drug or device when making treatment decisions”* is provided without compromising data privacy. YODA helps coordination with the industry by analyzing every request for clinical data scientifically and in an accurate, unbiased and fair manner. The relevant product data is systematically examined by *“two separate qualified research groups”*. Furthermore, YODA contributes towards data transparency by *“making all patient-level clinical research data available for analysis by other external investigators”*. The model is designed to promote transparency and protect against industry influence. Companies submit all relevant product data to a YODA systematic analysis, after which an independent Steering Committee, which includes leaders in the field of clinical research and biomedical ethics, advises the YODA project team. The YODA project emphasizes that *“(their) leadership is committed to transparency, publication and making the data publicly available”*. Johnson & Johnson announced a partnership with YODA, in which they will share raw data from many of its clinical trials. This initiative is part of a broader shift in both the United States and Europe, where researchers and some regulators are increasingly frustrated by the lack of transparency surrounding many drug trials, and wish to publish the information openly.

⁵⁸ Bravo E *et al.*: Citation of bioresources in journal articles: moving towards standards. *European Science Editing* 2013; 39(2):36.

⁵⁹ EASE Guidelines for Authors and Translators of Scientific Articles to be Published in English www.ease.org.uk/publications/author-guidelines

⁶⁰ YODA Project, Yale University Open Data Access (YODA) Project: A New Approach to Data Access and Transparency <http://medicine.yale.edu/core/projects/yodap>

⁶¹ Ritchie J *et al.*: The Yale University Open Data Access (YODA) Project: Developing Methods for Sharing Clinical Trial Data. *Yale University and Yale-New Haven Hospital Center for Outcomes Research and Evaluation* 2014.

1.8. The international rare cancer initiative

An article published in *Expert Opinion on Orphan Drugs*⁶² discusses the current and future approaches of International Rare Cancer Initiative (IRCI, www.irci.info). This initiative began in 2011 to facilitate conducting international clinical trials for patients suffering from rare cancers. It now oversees eight clinical trials for seven types of rare cancers. The initiative does not provide funding to sponsors, but coordinates clinical research funders and networks, providing advice and assistance to researchers involved in these trials. From the start, IRCI was mostly interested in contributing to the analysis of clinical trials on limited participants and liaising with regulators and industry for commercial viability of the drugs. The article explains that some statistical methods account for systematically small participant numbers. While conducting clinical trials internationally is critical, this also presents various levels of complexity that must be dealt with. If trials span across borders, several challenges arise, such as quality control of these clinical trials and access to the drugs during clinical trials. The authors mention other challenges that must be overcome, namely regulatory challenges that differ in different countries, such as access to specific expertise and the procedure required in case the clinical trial is a success. The article also touches upon funding requirements for these categories of clinical trials. Finally the authors note that “*measures should be taken to improve the integration of research across international boundaries, to improve the funding of academic research and to better integrate the research capacity of industry with the public sector for the greater benefits of patients and society*”.

1.9. CLARITY Challenge

In March 2014, Kohane *et al.* reported on the CLARITY Challenge⁶³ in *Genome Biology*⁶⁴, which sought to develop standards to analyze, interpret and report clinical sequencing to diagnose genetic disorders. The study challenge included information on twelve individuals from three families with different heritable disorders. Clinical information was provided through medical records, exome sequencing using the sOliD platform and whole-genome sequencing by complete genomics. Thirty international groups participated in the challenge and were assessed on the basis of the methods they used for analysis and interpretation. The groups were assessed on whether the methods were efficient, scalable and replicable, and on the clinical utility of their case reports. Only two groups identified the consensus candidate variants in all the cases, although there was significant overlap in the candidates reported across the teams. Consensus emerged on the methods used for alignment, variant calling and pathogenicity prediction. For instance, most the groups used gatK and saMtools, either alone or in combination, for variant calling and used both siFt and PolyPhen for pathogenicity prediction. The authors highlighted the need for broader adoption of standard

⁶² Negrouk A, Lacombe D, Trimble EL, Seymour M: Clinical research for rare cancers: is it a reality in the global regulatory landscape? The international rare cancer initiative. *Expert Opinion on Orphan Drugs* 2014; 2(5): 433-440.

⁶³ Boston Children’s Hospital: CLARITY Challenge <http://www.childrenshospital.org/research-and-innovation/research-initiatives/clarity-challenge>

⁶⁴ Brownstein CA *et al.*: An international effort towards developing standards for best practices in analysis, interpretation and reporting of clinical genome sequencing results in the CLARITY Challenge. *Genome Biology* 2014; 15(3): R53.

data formats, consideration of coverage along with an estimation of false negative rates for candidate genes and further development of publicly available genomic databases.

1.10. Mitoseek

Due to advances in next generation sequencing, a whole genome can be sequenced in a matter of days, providing immense information on the genome. A significant amount sequenced DNA belongs to the mitochondrial genome, and while unintentionally sequenced, this information can provide researchers “*with unique opportunities to study the mitochondrial genome*”. In order to help researchers study the mitochondrial genome effectively, researchers from Vanderbilt University have created an open-source software tool called MitoSeek (github.com/riverlee/MitoSeek). This unique genome analysis tool can “*reliably and easily extract mitochondrial genome information from exome and whole genome sequencing data*”. Researchers can get myriad types of information including “*mitochondrial genome alignment quality, estimates relative mitochondrial copy numbers, and detects heteroplasmy, somatic mutation, and structural variants of the mitochondrial genome*”. Some drawbacks of this software include its capacity to calculate only relative mtDNA copy numbers, as opposed to absolute mtDNA copy numbers, and its ability to detect large copy number variations. Notwithstanding the drawbacks, MitoSeek is a unique software that creates opportunities for high throughput mitochondrial sequencing data-mining from existing large exome sequencing databases. The algorithm used to construct this website and a short description was published in an article in *Bioinformatics* in 2013⁶⁵.

1.11. Global Rare Diseases Patient Registry and Data Repository (GRDR)⁶⁶

In 2012 the Office of Rare Diseases Research launched a pilot project to establish the Global Rare Diseases Patient Registry and Data Repository (GRDR grdr.ncats.nih.gov). The goal is to establish a data repository of de-identified patient data, aggregated in a standardized manner, to enable analyses across many rare diseases and facilitate various research projects, clinical studies and clinical trials. The aim is to facilitate drug and therapeutics development, and to improve rare disease patient quality of life. Ongoing activities expanded the initiative to include collaborations with colleagues in EU countries, Japan, Australia and other nations.

1.12. Pathophenotypic Similarity Gene Network (PSGN)

In an article published in February 2013 in *PLoS One*⁶⁷, the authors created a Pathophenotypic Similarity Gene Network (PSGN) associating clinical features (pathophenotypes) with disease causing genes. They then compared this with gene-to-gene

⁶⁵ Guo Y, Li J, Li C, Shyr Y, Samuels DC: MitoSeek: extracting mitochondria information and performing high-throughput mitochondria sequencing analysis. *Bioinformatics* 2013; 29(9): 1210-1.

⁶⁶ Forrest CB *et al.*: The case for a global rare-diseases registry. *The Lancet* 2010; 377(9771): 1057-1059.

⁶⁷ Reyes-Palomares A *et al.*: Global Analysis of the Human Pathophenotypic Similarity Gene Network Merges Disease Module Components. *PLoS-One* 2013; 8(2):e56653.

network models such as ‘the human disease network’⁶⁸ and ‘the orphan disease networks’⁶⁹ and found that this model helped reveal gene pairs with significant similarity based on several criteria were previously overlooked. To illustrate their model, the authors mapped all the phenotypes and their corresponding genes associated with maple syrup urine disease (MSUD) to prepare a merged pathological module. The authors believe that the “*pathophenotypes contribute to identify underlying co-dependencies among disease-causing genes that are useful to describe disease modularity*”.

1.13. PhenomeNet⁷⁰

PhenomeNet (phenomebrowser.net) was described in an article published in *Interface Focus*⁷¹ in April 2013 as an “*approach for integrating phenotypes across species and identifying candidate genes for genetic diseases based on the similarity between a disease and animal model phenotypes*”. According to the authors, PhenomeNet differs in its approach by not relying on ‘guilt by association’ but instead by evaluating phenotypes in relation to suggested candidate genes which may be used to study molecular mechanisms leading to certain rare diseases. The authors highlight that, in addition to disease phenotypes from the Online Mendelian Inheritance in Man (OMIM) database, the clinical signs from Orphanet have been integrated into PhenomeNet, allowing PhenomeNet to resourcefully identify known candidate genes for rare diseases. According to the authors, this study demonstrates that “*integration and computational analysis of human disease and animal model phenotypes using PhenomeNet has the potential to reveal novel insights into the pathobiology underlying genetic diseases*”.

1.14. Proposal for international guidelines on conducting research and sharing genomic data

In June 2014, Sugano published a proposed International Code of Conduct for Genomic and Health-Related Data Sharing in *The HUGO Journal*⁷². Earlier in 2014, Knoppers *et al.* recommended, in an article published in *Human Genetics*⁷³, that a Code of Conduct be drawn up to promote data sharing within a human rights framework. The latest draft of the Code was designed, under the aegis of the Global Alliance for Genomics and Health, by a consortium of research, patient advocacy, policy and bioethics communities including the Biobank Standardisation and Harmonisation for Research Excellence project (BioSHaRE, www.bioshare.eu), International Cancer Genome Consortium (ICGC, icgc.org), IRDiRC, International Society for Biological and Environmental Repositories (ISBER, www.isber.org),

⁶⁸ Kwang-Il G *et al.*: The human disease network. *PNAS* 2007; 104(21): 8685-8690.

⁶⁹ Zhang M *et al.*: The orphan disease networks. *American Journal of Human Genetics* 2011; 88(6): 755-66.

⁷⁰ Hoehndorf R, Schofield PN, Gkoutos GV: PhenomeNET: a whole-phenome approach to disease gene discovery. *Nucleic Acids Research* 2011; 39(18): e119.

⁷¹ Hoehndorf R, Schofield PN, Gkoutos GV: An integrative, translational approach to understanding rare and orphan genetically based diseases. *Interface Focus* 2013; 3(2).

⁷² Sugano S: International code of conduct for genomic and health-related data sharing. *The HUGO Journal* 2014; 8: 1.

⁷³ Knoppers BM *et al.*: A human rights approach to an international code of conduct for genomic and clinical data sharing. *Human Genetics* 2014; 133(7): 895-903.

Human Heredity and Health in Africa Initiative (H3Africa, h3africa.org) and Public Population Project in Genomics and Society (P3G, p3g.org) among others. Based on four founding principles regarding health, respect, research and transparency, the Code proposes guidelines to conduct research and share genomic data internationally with respect for human privacy and non-discrimination rights. Besides ethical values and the wish to avoid data misuse, the guidelines are designed to adapt to evolving genomic science and data sharing practices. The Code aims to establish a legal framework to be adopted by research organizations, institutions and industry conducting work using genomic and health-related data. In a spirit of wide collaboration, the authors of the Code invited anyone concerned to submit feedback on the draft until 1st July, before finalizing the Code for implementation.

III. RECENT INFRASTRUCTURES TO SPEED UP R&D

1. New infrastructures and databases contributing to speed up R&D

1.1. Publication of a map of human metabolism

Recon 2, the most comprehensive map of human metabolism is now available. Recon 2, is a community-driven, consensus representation of human metabolism. This map of metabolic interactions has been constructed after several “jamboree meetings” where experts “refined and consolidated biochemical knowledge from existing reconstructions and published literature”. Recon 2 which builds on Recon 1⁷⁴ is a comprehensive metabolic resource as well as an effective predictive model for inborn errors of metabolism (IEM) as it has predicted changes in metabolite biomarkers for 49 IEMs with 77 percent accuracy when compared to experimental data. Additionally, Recon 2 has also mapped exometabolomic data, protein expression data and allows comparative analysis of cell type specific models. Recon 2 has not mapped the entire human metabolism as it includes 1,800 out of approximately 20,000 protein-coding genes in the human genome. This map must be constantly updated, as empirical evidence becomes available, to expand its coverage. The process utilized to construct this metabolism map as described in Thiele *et al.*'s article *Nature Biotechnology*⁷⁵ and the tool is freely available at humanmetabolism.org. The authors believe that Recon 2 will facilitate future biomedical studies and help identify the most effective treatment modalities for various diseases.

1.2. Publication of ORDO, an ontology of rare diseases

The much awaited ontology of rare diseases was released in February 2014⁷⁶. Jointly developed by Orphanet and the European Bioinformatics Institute (EBI, www.ebi.ac.uk), the Orphanet Rare Disease Ontology (ORDO, www.orphadata.org) provides a structured vocabulary for rare diseases, capturing relationships between diseases, genes and other pertinent features, in a language directly understandable by computers. This is an all-inclusive and singular resource point for the ontological analysis of rare diseases. Due to the substantial advances in genome technology in recent decades, we are now witnessing an increasing complexity of genetic data with greater dispersion of phenotypic data in clinical databases. Additionally the intricacy and multiplicity of scientific and medical terminologies requires the need for reference tools that integrate normalized data for use by systems health information and research. The Orphanet database is world renowned for integrating rare disease nosology (classification of rare diseases), their relationships (gene-disease relations, epidemiological data and orphan drugs) and connections with other terminologies (MeSH, SNOMED CT, UMLS), genes, non-coding RNA loci related diseases connected to

⁷⁴ Duarte *et al.*: Global reconstruction of the human metabolic network based on genomic and bibliomic data. *PNAS* 2007; 104(6): 1777-1782.

⁷⁵ Thiele *et al.*: A community-driven global reconstruction of human metabolism. *Nature Biotechnology* 2013; 31: 419-425.

⁷⁶ Editorial: The much awaited ontology of rare diseases has just been released. *OrphaNews*, 20 February 2014
<http://www.orpha.net/actor/EuropaNews/2014/140220.html#Edito>

scientific databases (HGNC, OMIM, UniProt, GenAtlas, Reactome, Ensembl, IUPHAR) and other classifications (ICD10).

This data is freely downloadable on a solid platform through Orphadata. The partnership with EBI has facilitated modelling rare disease information, generating an ontology with a robust and consistent structure revealing significant relationships. In particular, it contains semantic relationships between genes and diseases: causal germ or somatic mutations, modifier genes, susceptibility genes, fusion genes involved in causation of tumors and genes with a major role in the phenotype of chromosomal abnormalities. This assists researchers as they can review rare disease relationships and classifications globally, and facilitates cross referencing with other ontologies. Additionally, it is characterized by interoperability with other resources used by genetic databases. Thus, this alliance provides bioinformaticians and researchers a method to understand the associations between wide-ranging data in a standardized format integrated into other IT environments. Orphanet classifications can be browsed in the Ontology Lookup Service (OLS, www.ebi.ac.uk/ontology-lookup). The Orphanet Rare Disease Ontology is updated monthly following the OBO guidelines on deprecation of terms. This ontology is available to all on BioPortal (bioportal.bioontology.org), EBI and Orphadata.

1.3. PhenomeCentral: a new matchmaking web portal^{77,78}

Due to the availability of low-cost genome sequencing, the identification of the molecular cause of hundreds of rare genetic disorders can be an achievable goal. However, the discovery of disease-causing variants requires confirmation of the mutation in multiple unrelated individuals. Additionally, an even larger number of genetic disorders remain unsolved due to the difficulty of identifying second families. It is therefore critical to establish effective and secure data-sharing techniques that allow clinicians and scientists to identify additional families via phenotype and genotype searches. To address this need, PhenomeCentral (phenomecentral.org), co-led by Michael Brudno and Kym Boycott, and developed by the Centre for Computational Medicine at the Hospital for Sick Children (ccm.sickkids.ca) in Toronto, Canada, was launched on Rare Disease Day (28 February 2014). PhenomeCentral is a novel online system that matches patients with similar genotypes and phenotypes. Its aim is to connect clinicians and scientists worldwide working on similar cases and speed up the discovery of genes responsible for rare disorders. Michael Brudno, Associate Professor at the University of Toronto's Department of Computer Science, explained how this portal will work: *"PhenomeCentral securely stores clinical and genetic information on patients with undiagnosed rare diseases. Clinicians will upload information and the database will automatically and anonymously match patients with similar genome and phenotypes. This will enable faster diagnoses and simpler identification of the genetic*

⁷⁷ PhenomeCentral "matchmaking" portal launched on Rare Disease Day 28 February 2014 <http://rd-connect.eu/news/2014-02-28-phenomecentral-matchmaking-portal-launched/>

⁷⁸ One-of-a-kind web portal created to bolster research and treatment for rare diseases <http://web.cs.toronto.edu/news/current/rarediseaseportal2014.htm>

cause of rare diseases.” Dr. Kym Boycott, geneticist and senior scientist at the Children’s Hospital of Eastern Ontario (CHEO) added that *“together, researchers around the world are going to successfully crack the code for thousands of patients with unsolved conditions.”* PhenomeCentral is funded by the Canadian Institutes of Health Research (CIHR), Genome Canada, the Ontario Genomics Institute, as well as the Natural Sciences and Engineering Research Council (NSERC) through the Collaborative Health Research Program. Global partners of PhenomeCentral include the NIH Undiagnosed Diseases Program (US), CARE for RARE (Australia), Finding of Rare Disease Genes (Canada), RD-Connect (Europe and Australia) and IRDiRC.

1.4. The Developmental Brain Disorders Database

A new database that references the ontology of developmental brain phenotypes was described in an article published in *American Journal of Medical Genetics*⁷⁹ in 2014. The Developmental Brain Disorders Database (DBDD, www.dbdb.urmc.rochester.edu) is a *“publicly available, online-curated repository of genes, phenotypes, and syndromes associated with neuro-developmental disorders”*. According to the authors, DBDD uses a novel system of levels of evidence for gene-phenotype associations that will assist clinicians to correctly identify neurodevelopmental phenotypes, recognize syndromes and prioritize the best candidate for genetic testing. The database will also provide researchers efficiently documented gene sources against which sequencing results can be compared and provide observations on the neurogenetics knowledge base landscape. Phenotype definitions in DBDD are drawn from the Medical Subject Headings controlled thesaurus (MeSH), the Human Phenotype Ontology (HPO), peer-reviewed publications indexed in PubMed and key textbooks in neuroradiology, medical genetics and epilepsy. The authors believe DBDD will streamline neurodevelopmental disorder understanding when used with existing web-based resources such as OMIM and GeneReviews. DBDD is expected to introduce levels of evidence for gene-phenotype associations and a structured ontology of neurodevelopmental disorders. The authors further highlight the user-friendly nature of this updatable database and its ability to provide consistent phenotype terminologies. DBDD is hosted at Rochester University’s Medical Center.

⁷⁹ Mirzaa GM *et al.*: The Developmental Brain Disorders Database (DBDD): A curated neurogenetics knowledge base with clinical and research applications. *American Journal of Medical Genetics Part A* 2014; 164(6): 1503-1511.

IV. TRENDS

1. Trends in the field of therapy development

1.1. A new model for the drug development pipeline

An article published in *Science Translational Medicine*⁸⁰ suggests revamping the drug development model and suggests a comprehensive new model. According to the authors, inadequacies in the drug development system hamper the process, resulting in significant losses of potential drug approvals. This is detrimental to patients waiting for rare disease treatments. The authors reject the linear model of drug development which they believe to be grossly oversimplified and defunct. They propose a model called Navigating the Ecosystem of Translational Sciences (NETS) “*that is sufficiently complex*” with a “*collection of interconnected processes with iterative feedback loops, rather than a series of discrete steps but allows these normally disparate players to assemble*”. This model, according to the authors, mirrors the needs of 21st century drug development as the process incorporates all stakeholder interests. The model emphasizes that for successful drug development it is imperative that basic science, therapeutic target discovery, nonclinical research, regulatory science and clinical research function collaboratively. In addition to revamping the current model, the author also suggests changes in the existing grant system to encourage novel research for current needs.

1.2. A case for regulators: Monogenic Protein Replacement Therapies

An article published in *Science Translational Medicine*⁸¹ in 2013 discusses the high percentage of approval rate of Monogenic Protein Replacement Therapies (MPRT) making a case for expanded investment into MPRTs. The authors analyzed the regulatory approval rates of MPRTs compared to other orphan drugs and other drug classes and show that over 85 percent of MPRTs are approved. The authors ascribe the regulatory success of MPRTs to high understanding of “*clinical pathogenesis, mechanism of action and ability to manufacture the MPRT*” blood components and many lysosomal enzymes. MRPT studies therefore require smaller clinical trials. The authors recognize that the probability of MPRT success to treat lysosomal or blood disorders is high due to the amount of research on the mechanisms of action for this disease.

⁸⁰ Baxter C *et al.*: An End to the Myth: There Is No Drug Development Pipeline. *Science Translational Medicine* 2013; 5(171): 171cm1.

⁸¹ Gorzelany JA, de Souza MP: Protein Replacement Therapies for Rare Diseases: A Breeze for Regulatory Approval? *Science Translational Medicine* 2013; 5(178): 178fs10.

1.3. Demonstration that orphan and non-orphan drugs are treated the same by EU regulators

An article in *Drug Discovery Today*⁸² demonstrates the existence of strong similarity in the way orphan and non-orphan drugs are reviewed and assessed in the European regulatory marketing authorization system. The authors compared marketing authorization applications of seventeen orphan drugs (ODs) and fifty-one non-ODs evaluated by the European Medicines Agency (EMA) in the period 2009–2010. They specifically attempted to identify differences between ODs and non-ODs in number and type of deficits brought forward during the EMA review, regarding the clinical development plan, clinical outcome and medical need. They studied whether these deficits were similarly associated with marketing approval in the EU. The authors found differences in deficits, but also found similarities in the way ODs and non-ODs were reviewed and marketing approval decisions were taken, underlining the equally high regulatory standards between the two. The authors established that in the majority of licensed ODs, approval was based on robust randomized clinical trials and endpoints that were considered clinically relevant. The authors found differences between ODs and non-ODs in the area of "*study design (i.e. use of single arm studies), clinically relevant endpoint (i.e. more challenging for ODs), finding the appropriate target population (i.e. for ODs less a challenge than for non-ODs), safety profile (i.e. for most ODs less favorable), acknowledged high medical need (i.e. in two third of ODs dossiers, one fifth of the non-ODs dossiers)*". They argued that these differences are due to the limitations inherent to studying rare diseases as original OD submissions are based on smaller studies. However, the EMA identified and weighted deficits (i.e. concerns, doubts and objections) rather than the study design characteristics. This study shows that the EMA does not accept lower levels of evidence (development and outcome) for ODs and non-ODs, unless this could be adequately justified by the applicant, when limited opportunities for further research allowed exceptional approval or when the company committed to add additional data to meet the standards of drug development that EMA requires and the OD was conditionally approved.

1.4. Dissection of challenges and opportunities of drug repositioning

An article in *Trends in Pharmacological Sciences*⁸³ addresses the issue of drug repositioning, an especially important topic to discuss for orphan drug developers. According to the author "*This is an innovation stream of pharmaceutical development that offers advantages for drug developers along with safer medicines for patients*". In this article, the author provides examples of drugs that have been successfully repositioned and gained new indications, and discusses the challenges that come with drug repositioning. The author believes that a repositioned drug with proven known safety has economic, social and ethical benefits. The author provides a revised model for effective drug repositioning.

⁸² Putzeist M *et al.*: EU marketing authorization review of orphan and non-orphan drugs does not differ. *Drug Discovery Today* 2013; 18(19-20): 1001-6.

⁸³ Novac N: Challenges and opportunities of drug repositioning. *Trends in Pharmacological Sciences* 2013; 34(5): 267-72.

1.5. Orphan drug report forecasts worldwide orphan drug sales to double by 2018

An optimistic future for orphan drugs is predicted by a study conducted by EvaluatePharma⁸⁴ published in 2013. The laws adopted in the US, EU and Japan to encourage research and development of orphan drugs provided significant incentives to pharmaceutical companies developing orphan drugs. These incentives included fee reductions, reduced R&D costs and most notably market exclusivity for a significant period of time (seven years in the US, ten in the EU). Since then, orphan drug production has been considered lucrative by many biotechnology companies. The EvaluatePharma report shows a steady increase in orphan drug sales over the years and has forecast that worldwide orphan drug sales will double to 15.9 percent by 2018. The report identifies Novartis as leader of the orphan drug sales market in 2018 with Roche, Celgene, Pfizer and Sanofi in the next four positions. The number one orphan drug in 2018 is predicted to be Roche's Rituxan, indicated for the treatment of rare diseases non-Hodgkin lymphoma and chronic lymphocytic leukemia. A close second is Revlimid (Celgene) for the treatment of multiple myeloma and myelodysplastic syndromes.

The report has envisaged the return on investment (ROI) for orphan drugs to be considerably higher than that of non-orphan drugs (10.3 times and 6 times greater than investment, respectively) which makes orphan drugs a more lucrative option for research and development. This increase in ROI is due to reduced patient numbers for an orphan drug clinical trial, the expected increase in worldwide drug sales as well as shorter approval times due to priority review provided to orphan drugs in the US. The increase in ROI does not take into account the tax credits that are provided to orphan drug developers in the US. It should be noted that the time taken for Phase III trials does not differ between orphan and non-orphan drugs. Based on the ROI calculation, the report identifies Lilly's anti-VEGF α MAb IMC-1121B, Roche's anti-mesenchymal epithelial transition (c-Met) MAb and Pharmacyclics' Ibrutinib to be the top three most valuable orphan drugs in 2018. However, the report identified Kyprolis, indicated for multiple myeloma, as the most promising new orphan drug in 2012 with expected sales of US\$897 million by 2017, with Kalydeco indicated for cystic fibrosis as a close second. The report also highlights the strong increase in the number of orphan designations accumulated in the US, EU and Japan since 2003. The report indicates that 18.5 percent of designations in the EU are for ultra-rare diseases (prevalence of 1/10,000 or less). Acute myeloid leukemia has the greatest number of orphan drug indications, followed by blood malignancies and other well-defined rare diseases such as cystic fibrosis and Duchenne muscular dystrophy. This report further informs on the potential of orphan drugs in the market and provides an impetus to pharmaceutical companies to go forward with research and development for orphan drugs and medicinal products.

⁸⁴ EvaluatePharma: Orphan Drug Report 2013 <http://www.evaluategroup.com/public/reports/EvaluatePharma-Orphan-Drug-Report-2013.aspx>

1.6. Study of orphan medicines market uptake finds substantial variation across Europe

An article published in the *Journal of Clinical Pharmacy and Therapeutics*⁸⁵ reports observations on the variations in orphan medicinal product availability across Europe, examining how two particular factors affect market uptake of orphan products: gross domestic product (GDP) and the availability of a formal Health Technology Assessment (HTA) organization to inform reimbursement and policy decisions. Analyzing sales data from twenty-three EU countries between 2001 and 2010, using the IMS Health database, the authors looked at the number of drugs launched and sales and volume uptake of seventeen selected orphan medicines. Countries with a higher GDP enjoyed a greater availability of orphan drugs, independent of the existence of an HTA organization. For countries with a lower GDP and for those with an HTA organization, a lower rate of orphan drug availability was observed. The study reveals the wide heterogeneity in HTA practice among EU Member States and suggests that initiatives such as the Clinical Added Value of Orphan Medicinal Products (CAVOMP) project could help facilitate the uptake of orphan drugs across Europe. A recommendation was to be adopted by the European Union Committee of Experts on Rare Diseases.

1.7. Analyzing cost-effectiveness of Orphan Drugs: suggestions for the future

In an article published in *Applied Health Economics and Health Policy*⁸⁶, the authors discuss several approaches to tackling the decision of the Dutch Healthcare Insurance Board advice on not reimbursing orphan drugs (enzyme replacement therapy) that target lysosomal storage disorders (agalsidase alfa and agalsidase beta for Fabry disease and alglucosidase alfa for Pompe disease). The Dutch Healthcare Insurance Board concluded this on the basis of the “*unfavorable cost effectiveness originated from the limited additional therapeutic value (as a result of the slow progression of the disease) and high costs*”. Additionally continued reimbursement of these drugs would lead to limited resources for other drugs which may be more cost-effective. Reimbursement of drugs based on cost-effectiveness has been a topic of intense debate due to scientific and political challenges. According to the authors, cost-effectiveness concerns of orphan drugs is due to the inherent uncertainty around its the safety and effectiveness at the time of market launch owing to small numbers of clinical trial subjects, lack of randomized controlled trials and the use of surrogate efficacy measures. The authors believe guidelines on analyzing and assessing cost-effectiveness of orphan drugs for (ultra-)rare diseases are needed, such as the National Institute for Health and Clinical Excellence’s (NICE) guidelines to assess orphan drugs in England and Wales from April 2013⁸⁷. To address the issue of low numbers of patients in the Netherlands, the proposed launch of a “*compulsory European wide registry following marketing authorization of an orphan drug*” is encouraged by the authors. According to the authors, addressing

⁸⁵ Picavet E *et al.*: Market uptake of orphan drugs – a European analysis. *Journal of Clinical Pharmacy and Therapeutics* 2012; 37(6): 664-667.

⁸⁶ Simoens S *et al.*: Cost-Effectiveness Assessment of Orphan Drugs. *Applied Health Economics and Health Policy* 2013; 11(1): 1-3.

⁸⁷ Department of Health and The Rt Hon Earl Howe: NICE to assess high cost low volume drugs; NICE are to take forward work to assess very high cost drugs for people who suffer with rare conditions. 19 July 2012 <https://www.gov.uk/government/news/nice-to-assess-high-cost-low-volume-drugs>

economic evaluation will involve approaches such as “*variable cost-effectiveness thresholds (which would set a higher threshold for orphan drugs) or weighted cost-effectiveness ratios (where the health gain in a patient with a rare disease would receive a higher weight)*”. They recommend further research to unravel societal values about orphan drugs and incorporate these into the decision-making process.

1.8. Review of eleven orphan drugs reveals scope for studying cost-effectiveness

The authors of a study published in *Orphanet Journal of Rare Diseases*⁸⁸ review the available evidence on clinical effectiveness, cost-effectiveness and budget impact of orphan drugs. The authors analyzed 338 studies in PubMed, Embase, NHS EED and HTA databases for eleven in-patient orphan drugs listed on the orphan drugs Dutch policy rule. The authors analyzed the drugs that met inclusion criteria for this study. According to the authors, 96 percent of the studies focused on clinical effectiveness of the drug, of which 41 percent were case studies while 39 percent observational studies. However, the authors observed that for all orphan diseases, at least one experimental or quasi-experimental study was found, and a randomized clinical trial (RCT) was available for over half the orphan drugs studied. Eight studies described the cost-effectiveness of an orphan drug and an equal number described an orphan drug’s budget impact. The authors exposed the often heard claim that RCTs are not feasible for orphan drugs. They discovered that RCTs were available in 60 percent of investigated orphan drugs. The authors highlight that since cost-effectiveness and budget impact analyses for orphan drugs are seldom published, assessing the effectiveness of orphan drugs, policy makers should expect an international interventional study to be available. They also inform policy makers to not expect country-specific RCTs to be carried out. Concerning cost-effectiveness assessment and budget impact of treatments, policy makers should not expect to find large bodies of evidence in the literature. The authors recognize that policy makers are restricted to evidence submitted by pharmaceutical companies or to coverage with evidence development schemes. Whether the available evidence is considered to be sufficient depends on the role of evidence based medicine in reimbursement decisions. The authors strongly urge for further research to examine the relation between available evidence and positive reimbursement decisions.

1.9. Impact of disease prevalence upon health technology assessment

Health technology assessment (HTA) methods evaluate drug reimbursement criteria and are expected to play an increasingly important role in drug reimbursement decisions as national economies come under pressure to optimize resources. HTA organizations provide guidance based on analysis of “*new treatment paradigms and health technologies, and the prevalence studies which determine when a disease is a current or future burden for patients and the community*”. An article published in 2013 in *Best Practice & Research Clinical*

⁸⁸ Kanters TA *et al.*: Systematic review of available evidence on 11 high-priced inpatient orphan drugs. *Orphanet Journal of Rare Diseases* 2013; 8: 124.

*Gastroenterology*⁸⁹ analyzed studies on strategies and healthcare policy to evaluate approaches impacting HTA decisions. The authors emphasize the *"utilization of the predictive values of screening tests that include prevalence in their calculations and analysis of all options for screening strategies necessary in HTA"*. According to the authors, it is necessary for cost-effectiveness analyses and statistical models to account for unforeseen consequences that may affect annual healthcare budgets, such as the emergence of new technologies.

1.10. Study describes the use of Multicriteria Decision Analysis for Valuing Orphan Medicines

An article published in 2013 in *Orphanet Journal of Rare Diseases*⁹⁰ studied the use of multi-criteria decision analysis (MCDA) to establish and apply a framework of weighted attributes to value orphan medicinal products. The study involved literature searches on the natural history and burden of forty rare diseases. The authors examined how payers assess treatment value based on three workshops involving GlaxoSmithKline managers working on orphan medicinal products, European Union clinical and health economics experts and representatives of rare diseases patient groups in the EU. The authors identified eight non-monetary criteria and weights, four of which were attributed to the disease and four to the treatment. Patient group representatives weighted patient and carer quality of life more heavily than the experts did. According to the authors, the multi-criteria decision analysis approach could be developed to be utilized by payers and health technology assessment bodies. The authors stated that *"given the intrinsically complex nature of the rare diseases and OMP environment, an MCDA approach for rare disease treatment value assessment has the merit of ensuring shared understanding of the elements of value as well as a clear articulation of trade-offs between those elements"*. The authors have piloted such an approach with patient group representatives and clinical and health economics experts who advise HTA bodies and payers. They believe the MCDA approach offers a possible basis for more comprehensive guidance to HTA, and pricing and reimbursement decision making.

1.11. COMPASS: a tool to assess clinical evidence of orphan medicinal products

The assessment of quality of evidence in small populations is often complex while generic tools remain unfit. A study published in 2013 in *Orphanet Journal of Rare Diseases*⁹¹ described the development and validation of a new tool named COMPASS to help assess clinical evidence of Orphan Medicinal Product (OMP) quality. The authors believe this tool can be *"applied to assess the quality of evidence of an OMP based on information in the registration dossier, for example by local reimbursement agencies, pharmacists or clinicians"*. According to them, the tool can contribute significantly towards making key decisions on

⁸⁹ Rotily M, Roze S: What is the impact of disease prevalence upon health technology assessment? *Best Practice & Research Clinical Gastroenterology* 2013; 27(6): 853-865.

⁹⁰ Putzeist M *et al.*: Drug development for exceptionally rare metabolic diseases: challenging but not impossible. *Orphanet Journal of Rare Diseases* 2013; 8: 179.

⁹¹ Picavet E *et al.*: Development and validation of COMPASS: clinical evidence of orphan medicinal products – an assessment tool. *Orphanet Journal of Rare Diseases* 2013; 8:157.

reimbursement and/or treatment on “*the principles of evidence-based decision making*”. The authors developed a three-part draft version of the COMPASS tool, based on data from the Orphanet website and EMA’s European Public Assessment Report (EPAR). The authors believe that the “*COMPASS tool does not attempt to score or rank the quality of clinical evidence, but rather to give an outline of various, key elements with respect to quality of clinical evidence of OMP studies*”.

1.12. Suggestions for successful clinical development for orphan indications

Conducting clinical trials for orphan indications is challenging for the drug developer as they have to circumvent problems such as rarity of patients, regulatory restrictions and scarcity of scientific research on rare diseases. An article published in 2013 in *Expert Opinion Orphan Drugs*⁹² outlines some of the main issues to consider when designing a clinical trial or clinical program for an orphan drug. The authors emphasize the importance of animal models, often lacking in rare disease research. Animal models facilitate the study of potential candidates for therapy and may impact the design of clinical trials when selecting dose and outcome measures. Lack of animal model studies may prevent early application for orphan designation, since evidence of effect, in preclinical or clinical studies, is generally required.

The authors highlight that many rare diseases have not been extensively studied and lack literature on their natural course. Much of the evidence is therefore often anecdotal or based on case studies, making it difficult to estimate the expected effect size of a therapy and to decide on the most appropriate duration for study. The authors call for a more thorough study of the etiology for rare diseases. The authors also point to the need for the regulatory officials to require the same level of proof of safety and efficacy for orphan drugs as for other drugs which can be complicated due to the small number of patients. The authors recommend using surrogate end points, which can be useful during a development program. The authors suggest that variability can also be controlled to some extent through appropriate statistical analysis methods. Another possibility would be to include placebo-controlled studies allowing crossover to a treatment intervention after a certain period of time or which provide long-term treatment follow-up that may alleviate concerns about access to potentially beneficial treatments.

1.13. Recommendations to select animal models for rare diseases: a compilation from EMA and peer-reviewed literature

A 2013 article published in *Nature Reviews Drug Discovery*⁹³ addresses “*the use of animal models in preclinical studies that are not closely based on the knowledge of the molecular pathology of the human disease*”. To assist researchers in determining an appropriate animal model that will reinforce success in preclinical trials, the authors have gathered current

⁹² Hall AK, Ludington E: Considerations for successful clinical development for orphan indications. *Expert Opinion on Orphan Drugs* 2013; 1(11): 847-850.

⁹³ Vaquer G *et al.*: Animal models for metabolic, neuromuscular and ophthalmological rare diseases. *Nature Reviews Drug Discovery* 2013; 12: 287-305.

knowledge of animal models used to study treatments for orphan diseases. In this review the authors focus on animal models for rare metabolic, neuromuscular diseases and ophthalmological diseases. Most of the animal models described in this article have been a part of preclinical research for medicinal products submitted to the EMA's Committee for Orphan Medicinal Products (COMP). This review provides the reader with information on a "*broad range of animal models (from small transgenic rodents to large animals with naturally occurring disease)*" that can be used for preclinical research. The authors illustrate animal models that are currently suitable for preclinical research and also the ones that may need improvement. Although a variety of animals are used in preclinical studies, most are rodents (mice and rats) as they are economical to maintain and because most of the transgenic research data is on rodents and not on larger animals. The authors emphasize however that "*there are limitations associated with the use of rodent models of disease, including their size and pathophysiological parameters*".

The authors recommend the correct use of larger animals when rodents are unable to provide results that can be correctly extrapolated for human applications. Another essential subject for success in preclinical trials, highlighted by the authors, is the "*rigorous application of statistics*". According to the authors, this aspect "*not only provides an accurate analysis of results but also improves experimental design increasing the chances of obtaining results that are robust*". For this purpose "*the EMA has published guidelines to help with trial design, hence facilitating clinical trials for rare diseases*". The authors also provide examples of models that can be used for advanced therapies (especially gene and cell therapy) as the EMA has considerable expertise in evaluating these. In conclusion, this review has provided an extensive analysis which will facilitate "*efficient and successful research and development of OMPs*".

1.14. Need to recognize the international scenario of clinical trials

In 2013, the journal *ecancermedicalscience* added articles to its website that explore the need for international collaboration on clinical trials. The editorial by Keat *et al.*⁹⁴, describes the International Rare Cancers Initiatives (IRCI), a joint initiative of the European Organization for Research and Treatment of Cancer (EORTC), the US National Cancer Institute (NCI), the National Institute for Health Research (NIHR) Cancer Research Network (NCRN) and Cancer Research UK (CR-UK). This initiative was established in 2011 to enable international collaboration for clinical trials for patients with rare cancers. This initiative encourages innovative trial designs and Bayesian statistics "*to maximize the potential for answering research questions and to identify and overcome barriers to international trials to allow agreed IRCI trials to run smoothly*". IRCI have identified nine rare cancers after consultation with clinical communities, where interventional strategies are possible. Seven communities are developing clinical trials for submission to funding. The authors mention in particular the progress made by the Gynecological Sarcoma Society who opened to

⁹⁴ Keat N *et al.*: International Rare Cancers Initiative (IRCI). *ecancer* 2013; 7: ed20.

recruitment a “Phase III randomized trial of gemcitabine plus docetaxel followed by doxorubicin versus observation for uterus-limited, high grade uterine leiomyosarcoma”. They are moving towards developing international collaboration for clinical trials worldwide.

1.15. Proposal of a new approach to pre-clinical research to boost academic and small enterprise orphan drug development

A 2012 article from *Orphanet Journal of Rare Diseases*⁹⁵ offers readers “A generalizable pre-clinical research approach for orphan disease therapy”. The authors propose a method that “relies on databases and computational analyses prior to the more expensive experimental validation of potential therapies”. Such an approach could side-step some of the costs and time of preclinical research. Access to “system-wide datasets, compounds and reagents for the orphan disorder research community, advances in both systems biology and computational prediction of small molecule-macromolecule interaction, the identification of additional generalizable therapeutic approaches” and further collaboration are listed as key steps for moving forward this approach.

1.16. Clinical development success rates of orphan drugs: high for phase I and II but low for phase III

*Nature Biotechnology*⁹⁶ published a comprehensive survey of clinical success rates of all FDA approved drugs which suggests that productivity may be even lower than previously estimated. The article addresses how successful orphan drugs have been over the years during the different phases of the FDA marketing authorization process. The authors report that although drugs for orphan indications have high rates of phase I and phase II success, phase III and New Drug Application (NDA)/Biologic License Application (BLA) success rates are similar to those of regular drugs. Orphan drugs can receive orphan status at all stages of development: preclinical, phase I, phase II, phase III and NDA/BLA. The authors found that orphan indications for phase I and II success rates were well above average. Orphan phase III success rates also compared favorably with all indications and orphan NDA/BLA approvals were lower. A subgroup analysis of phase III and NDA/BLA stage orphan drugs by indication reveals that the success rates of orphan drugs as oncological treatment were lower than non-oncology drugs with an orphan indication. The authors believe that some of the low phase III rates may be attributed to trial design factors and insufficient communication between sponsors and regulators during their end of phase II meetings. The authors recommend simultaneous improvements in basic science to increase clinical success rates. The authors believe their data is a warning to drug developers, regulators, investors and patients since FDA approval is granted for only one in ten drug indications that enter the clinic.

⁹⁵ Beaulieu CL *et al.*: A generalizable pre-clinical research approach for orphan disease therapy. *Orphanet Journal of Rare Diseases* 2012; 7: 39.

⁹⁶ Hay M *et al.*: Clinical development success rates for investigational drugs. *Nature Biotechnology* 2014; 32: 40-51.

1.17. Advances in human genetics are an opportunity for drug development

An article published in *Nature Biotechnology*⁹⁷ provides a perspective on human genetics as being the opportunity to innovate and improve clinical success rates in drug development. Genetic screens are comparatively unbiased and provide a causative link between a sequence variant and a phenotype. There is little doubt that genetics plays a major role in the risk (and pathogenesis) of most, if not all, common human diseases. The authors believe that once a pathogenic biochemical pathway has been pinpointed, researchers are able to correct or neutralize it. They can exploit the protein encoded by the gene variant as a drug target. Alternatively, they can act against other proteins in the same biochemical pathway or attempt to counter the destructive effects of the biochemical pathway by up- or down-regulating another pathway that affects the same physiologic function. The authors have performed a *post hoc* assessment of phase III successes and failures (for period 2000-2008) which supports their case for genetics as a positive predictor. All targets with clear genetic evidence and good pharmacologic agents in this set produce the clinical effect predicted by human genetics. The authors also provide other advantages of human genetics as they provide functional insights that liberate the target selection process from poorly predictive animal models. Genetic experiments can be designed without a priori assumptions about the nature of the disease as they are largely independent of models and hypotheses. This is particularly important for an industry whose business is declining. Genetically defined targets offer the opportunity to determine if candidate drugs directed against these targets can correct the biochemical defects before the launch of lengthy and expensive clinical endpoint trials. They may allow shorter, less expensive registration studies based on surrogate endpoints, rather than disease outcomes such as survival, as long as surrogate and outcome endpoints can be linked through convincing human genetics studies.

The authors have also provided an example where large and very costly clinical trials were performed in an attempt to show that agents that increase levels of HDL protect against coronary artery disease. The results suggest that raising HDL does not, by itself, affect the risk of getting cardiovascular diseases, but the discovery of a rare variant of proprotein convertase subtilisin/kexin type 9 (PCSK9), which lowers LDL cholesterol substantially and decreases the risk of early-onset heart attack, was an important advance. The authors highlight several pharmaceutical companies that have developed antibody inhibitors of PCSK9 and demonstrated that they lower levels of LDL cholesterol significantly in patients and are well tolerated.

⁹⁷ Kamb A, Harper S, Stefansson K: Human genetics as a foundation for innovative drug development. *Nature Biotechnology* 2013; 31(11):975-8.

1.18. Agreement to accelerate development, registration and access to medicines for rare diseases in the European Union through adaptive approaches

A paper published in the *Orphanet Journal of Rare Diseases*⁹⁸ describes how the EU can address the need to accelerate development and access to medications needed to treat rare disease patients. The article highlights that although a concerted discourse already exists between stakeholders, there is “growing recognition that the current research-and-development (R&D) and innovation-regulation ecosystem could be made more efficient to stimulate and support access to innovative therapies for those patients with rare, life-threatening diseases for which there are no adequate licensed therapies”. Despite the existence of mechanisms in Europe by which an orphan medicinal product (OMP) can currently be fast-tracked through the licensing system (such as granting a conditional marketing authorization or under exceptional circumstances), few OMPs have fulfilled the criteria to benefit from these mechanisms. The authors suggest adaptive licensing, involving a graded, tightly managed process, to enable faster entry of OMPs into the market and hence quicker access for patients. According to the authors, while there could be a risk of premature drug approvals on commercial rather than clinical grounds, patients, regulators and policy makers are in favor of adaptive licensing to accelerate OMP market entries.

1.19. Data sharing and transparency needed during orphan drug development and clinical trials

An article published in *Public Health Genomics*⁹⁹ demonstrates how data sharing from clinical trials can be key to the development and approval of medicines for rare diseases. The authors highlight how many events during the first half of 2013 have contributed to the movement for increased transparency. These include the development of the European Medicines Agency’s (EMA) new data publication policy, the creation of the AllTrials petition and GlaxoSmithKline’s choice to sign it, the launch of GlaxoSmithKline’s system for access to patient-level clinical trial data and Roche’s commitment to create a similar system, the release of results from the Yale University Open Data Access project’s first medicine analysis for Medtronic and the creation of the Reg4All website. The authors summarize major developments in clinical trial transparency between January and June 2013 and analyze the composition of datasets released by GlaxoSmithKline. GlaxoSmithKline’s database of available trials was tabulated and graphs of relevant trial characteristics were produced. The authors believe that, due to current transparency initiatives, additional data will likely become available over the next few years through systems similar to GlaxoSmithKline’s. Finally, the authors also highlight that although some aspects of GlaxoSmithKline’s model could limit its usefulness, the data currently listed is diverse and could be promising for researchers interested in rare disease treatment.

⁹⁸ Uguen D *et al.*: Accelerating development, registration and access to medicines for rare diseases in the European Union through adaptive approaches: features and perspectives. *Orphanet Journal of Rare Diseases* 2014, 9:20.

⁹⁹ So D, Joly Y, Knoppers BM: Clinical trial transparency and orphan drug development: recent trends in data sharing by the pharmaceutical industry. *Public Health Genomics* 2013; 16(6): 322-35.

1.20. Commercialization of gene therapy has stalled

An article published in *Gene Therapy*¹⁰⁰ examines the “commercialization of gene therapy in the context of innovation theories that posit a relationship between the maturation of a technology through its life cycle and prospects for successful product development”. The authors demonstrate that the “field of gene therapy has matured steadily since the 1980s”. The article reports an accumulation of “35,000 papers, 16,000 US patents, 1,800 clinical trials and US\$4.3 billion in capital investment in gene therapy companies”. “Gene therapy technologies comprise a series of dissimilar approaches for gene delivery, each of which has introduced a distinct product architecture”. “Using bibliometric methods, the authors quantified the maturation of each technology through a characteristic life cycle S-curve, from a Nascent stage, through a Growing stage of exponential advance, toward an Established stage and projected limit. The results show that capital investment in gene therapy is shown to have occurred predominantly in Nascent stage technologies and to be negatively correlated with maturity”. The authors maintain that “gene therapy technologies are now achieving the level of maturity that innovation research and biotechnology experience suggest may be requisite for efficient product development”. In conclusion the authors report that an “asynchrony between the maturation of gene therapy technologies and capital investment in development-focused business models may have stalled the commercialization of gene therapy”.

1.21. Use of Biomarkers to define orphan medicines designation in Europe

An article published in *Orphanet Journal of Rare Diseases*¹⁰¹ describes the use of biomarkers when assessing Orphan Medicinal Product (OMP) by the Committee of Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA). Biomarkers have been used widely by sponsors when submitting their application in order to define an orphan condition and to justify that the medicinal product under development fulfils the criteria for orphan designation. This has to be justified during both stages of OMP designation evaluation: at the time of orphan designation application and when the product is deemed a plausible therapy for a condition. The authors explain the role of COMP in assessing the use of biomarkers by sponsors of candidate orphan products according to three main areas: “to define the distinct medical condition or a valid sub-set for the designation to justify the intention to diagnose, prevent or treat a condition with a product, to determine significant benefit”. The authors are members of the COMP and discuss specific examples derived from their experience in which biomarkers have played a decisive role in assessing whether the candidate orphan medicines have provided a “plausible link to the condition” and the “exclusion of effects outside the subset”. Presentations and discussions from past submissions to the COMP, I

¹⁰⁰ Ledley FD *et al.*: Why commercialization of gene therapy stalled; examining the life cycles of gene therapy technologies. *Gene Therapy* 2014; 21(2): 188-94.

¹⁰¹ Tsigkos *et al.*: Use of biomarkers in the context of orphan medicines designation in the European Union. *Orphanet Journal of Rare Diseases* 2014; 9: 13.

which sponsors used biomarkers to support their request for orphan designation, elucidate how and when biomarkers are exploited by the COMP to assess OMPs.

1.22. Review addressing how FDA can further the development of medications for unmet needs

A state of the art review published in 2014 in *Clinical Pharmacology & Therapeutics*¹⁰² describes how the FDA set up special designation programs for orphan priority and fast track reviews and accelerated approval. These programs aim to expedite and sustain orphan drug development and facilitate authorization of new medicines for unmet medical needs through so-called ‘push–pull’ incentives. The author suggests that although generally successful over time, these designation programs have been confined to certain therapeutic areas and certain diseases within those areas. Nevertheless, the author notes that, despite considerable burden on research and development and public health needs, advances in research and disease knowledge are motivators for the FDA to intervene more actively in certain disease areas. The author describes “*the need for the FDA to make designation and implementation decisions with a view that reaches beyond the immediate horizons of political expediency and patient advocacy*”. The article highlights ways in which the FDA can “*encompass the broader expanse of factors that now influence R&D decisions—global competitiveness, the needs of investors, emerging sponsors, and patient-focused drug development*” in efforts to develop new medicines for special medical needs.

1.23. A bright future ahead due to advances in pediatric gene and cell therapy

A review published in 2014 in *Advanced Drug Delivery Reviews*¹⁰³ describes “*the range of possible gene and cell therapy applications which is expanding at an extremely rapid rate*”. Currently advanced therapy medicinal products (ATMPs) are on the cutting edge of novel medicines. In this article, the authors highlight the benefits pediatric patients with inherited conditions stand to gain from these novel therapies. It now appears plausible to develop a gene or cell therapy for a vast number of these diseases. The authors describe progress in various cell and gene therapies which are presently regulated in the EU under ATMP guidelines and divided into three categories: somatic cell therapy; gene modified cells; and xenotransplantation. The authors illustrate advances in the area of stem cell therapies and potential bench-to-bedside therapeutic pathways. They introduce key developments in advanced therapies for conditions affecting children, including corneal and retinal repair, pancreatic islet cell therapy, muscle repair and hematopoietic stem cell therapy adjuncts. The authors warn that, although several of the gene and cell therapies have received orphan drug designation, only four ATMPs have received marketing authorizations (Glybera, Epicel, Carticel and ChrondroCelect) and only one licensed gene therapy treatment (Glybera) despite twenty years of clinical trials. The authors state that challenges must be addressed

¹⁰² Milne C-P: Prospects for Rapid Advances in the Development of New Medicines for Special Medical Needs. *Clinical Pharmacology & Therapeutics* 2013; 95(1): 98-109.

¹⁰³ Buckland KF, Gaspar BH: Gene and cell therapy for children—new medicines, new challenges? *Advanced Drug Delivery Review* 2014; 73: 162-9.

to successfully deliver these therapies and demonstrate that their benefits outweigh developmental costs.

1.24. Pathway for Approval of a Gene Therapy Orphan Product to be better defined in the US

A commentary published in 2014 *Molecular Therapy*¹⁰⁴ describes the long strides made by the US FDA to augment the development and access to gene therapy products as well as recommendations for further improvement in regulation. The author notes that the FDA has yet to approve a gene therapy product but the recent approval of a rare disease treatment based on an adeno-associated virus (AAV) vector in the European Union sets the stage for similar programs to be presented to the FDA in the coming years. The author describes the current role of the FDA Safety and Innovation Act (FDASIA) to expedite the development and review of innovative medicines that address certain unmet medical needs. Additionally, the agency will strive to meet performance goals that include increasing interaction with drug sponsors during the review process and improving engagement with patients, specifically those with rare diseases. The author recommends rethinking the traditional approach of staged development that includes developing effective surrogate end points. A new approach is especially important when no alternative treatment is available and the disease burden is high. The author describes the role of FDASIA to expand the scope of products that qualify for fast-track status and accelerated approval. Medicinal products with ‘breakthrough therapy’ status include those intended for the treatment of a serious or life-threatening disease or condition for which there is an unmet medical need. While such products are recognized as beneficial, meeting the criteria for accelerated approval often remains a challenge. The author hopes that once these pathways are mastered by the gene therapy and rare-disease research community, many indications may gain gene therapy approval in the US, thus meeting the needs of the rare disease community.

1.25. Need to rethink the clinical trials of exon skipping therapy for DMD

Exon skipping is a promising therapeutic strategy for Duchenne muscular dystrophy (DMD) patients, but the road to drug approval is unclear. An article published in *Science Translational Medicine*¹⁰⁵ makes a case for early-stage de-risking and regulatory guidance for innovative strategies. The article focuses on exon skipping therapy to treat a DMD patient with antisense oligonucleotides directed against the dystrophin mRNA transcript, restoring the proper reading frame and thus protein production. Although early preclinical reports and mouse model studies were promising, phase III trials of this therapeutic approach carried out by GlaxoSmithKline (GSK), in partnership with Prosensa, failed to demonstrate significant improvement of the primary outcome measure—the 6-minute walk test. GSK has since terminated its partnership with Prosensa for the exon-skipping program in DMD. An alternative oligonucleotide therapy, using Sarepta’s morpholinos, demonstrated sound

¹⁰⁴ Byrne BJ: Pathway for Approval of a Gene Therapy Orphan Product: Treading New Ground. *Molecular Therapy* 2013; 21(8): 1465-1466.

¹⁰⁵ Hoffman EP, McNally EM: Exon-Skipping Therapy: A Roadblock, Detour, or Bump in the Road? *Science Translational Medicine* 2014; 6(230): 230fs14.

safety profiles in two small trials in DMD patients. They were not, however, granted accelerated approval by the FDA. The authors suggest that alternative methods to the 6-minute walk test, such as measures of strength, may be more accurate surrogate endpoint measures of potential drug efficacy. The authors observed that altering dose and chemistry at phase II trials increased and stabilized *de novo* dystrophin production in patient muscle. The authors believe that optimizing aspects of clinical trial designs (early age patient treatment, dose optimization and improvement of dystrophin protein measurement methods in patient muscle biopsies) could improve therapeutic approaches.

An article published in *Journal of Neurology*¹⁰⁶ explains the changing patterns of limb function in DMD patients, which in turn might help assess these patients. *“With increasing life expectancy, upper extremity (UE) function becomes more and more important in boys with DMD”*. In order to understand these changes, the authors distributed worldwide *“a Web-based questionnaire on UE function, covering all domains of the International Classification of Functioning Disability and Health”*. The authors found that *“UE pain, stiffness, and activity limitations increased with disease stage”*, despite which only a small number of the respondents used supportive aids. The authors suggest clinicians *“pay attention to UE limitations before DMD patients lose their capacity to walk”*, prescribe *“effective and adequate aids”* and focus attention on *“pain and stiffness in the therapeutic management to help reduce UE activity limitations and related restrictions in social participation”*.

1.26. Increasing role of rare disease patients/parents in drug discovery

An article published in *Drug Discovery Today*¹⁰⁷ emphasizes the vital role of parents and patients to *“fund, discover and develop treatments for rare and ultra-rare diseases”*. The article illustrates some of the success stories resulting from parent and patient involvement. Activities include entrepreneurship, advocacy and acting as principal investigators to further scientific knowledge leading to drug discovery. The authors highlight that a number of parents and patients leading initiatives have no formal scientific or medical education. Patients and parents play a significant role in disrupting *“the usual course of drug discovery”*, a process that traditionally requires years to develop appropriate therapies. The authors describe three ultra-rare disease parent/patient advocate groups involved in developing treatments for these diseases. They recommend this approach as an alternative model for pharmaceutical research. Parent/patient efforts have proved instrumental in drug discovery for rare diseases and for profitability of companies involved in developing and manufacturing these drugs. The authors highlight the *“urgent need to accelerate discovery and development for thousands of other rare and ultra-rare diseases”*. They encourage academic and pharmaceutical scientist to join parent/patient advocates to gain and share advice to accelerate rare disease medicinal product development. The authors also warn

¹⁰⁶ Janssen MM *et al.*: Patterns of decline in upper limb function of boys and men with DMD: an international survey. *Journal of Neurology* 2014; 261(7): 1269-88.

¹⁰⁷ Wood J: Multifaceted roles of ultra-rare and rare disease patients/parents in drug discovery. *Drug Discovery Today* 2013; 18(21-22): 1043-51.

that a balance is necessary for patient/parent involvement, concerning when they should become involved and when they should allow experts to take the lead. The authors believe that *“the lack of formal scientific or medical training should not hold people back in their search for researching or developing treatments”*.

1.27. Internet tools as effective methods to recruit rare disease patients into registries

The Internet offers investigators the opportunity to reach dispersed rare disease patients and communities in order to gather larger numbers for research. In an article published in the *American Journal of Medical Genetics*¹⁰⁸, Johnson *et al.* analyze methods of recruiting patients with rare diseases into online registries. During 2012, the authors recruited participants in a Neurofibromatosis type 1 (NF1) patient registry initiative (NPRI) to conduct clinical and epidemiological research. Using various Internet and clinical recruiting approaches, Johnson *et al.* assessed the impact of online recruitment methods on constituting rare disease registries. Methods of recruitment included paid advertising on Google and Facebook—targeting individuals based on keyword searches—, advocacy group postings, institutional websites, letters and pamphlets for distribution to patients in the US and Australia. During the one-year recruiting period, 76 percent of the 880 participants completed the NPRI questionnaire. Up to 70 percent of individuals discovered the initiative through Google and Facebook targeted advertising. On the other hand, fewer than 10 percent of participants heard of the initiative through healthcare providers, institutional websites or advocacy groups. The authors suggest, therefore, that advertising through social media websites is an effective tool to recruit larger numbers of rare disease patients from far reaching geographic areas into registries. While online advertising offers great potential, the authors nevertheless warn about the quality of recruited samples. They discovered their patient samples to be over represented by female participants, despite NF1 affecting male and female populations equally. The authors also draw attention to the occurrence of incomplete, duplicate or false registrations due to the lack of capacity to analyze Internet user profiles.

1.28. Do-it-yourself patient registries: Proposed user-friendly design software

In a 2014 article published in *Source Code for Biology and Medicine*¹⁰⁹, Bellgard *et al.* propose new features for rare disease registry frameworks (RDRFs) that allow non-professional software developers to generate and manage patient registries. As the number of identified rare diseases grows, the need for dynamic registries has become increasingly important to manage the quantity of information and data. The ability to exchange information between registries is also essential to develop and optimize patient databases. Most registries, however, are still constructed on static programs and data elements (DEs) requiring assistance from software developers. Exchanging information between registries

¹⁰⁸ Johnson KJ *et al.*: Evaluation of participant recruitment methods to a rare disease online registry. *American Journal of Medical Genetics Part A* 2014; 164(7): 1686-94.

¹⁰⁹ Bellgard M *et al.*: Second generation registry framework. *Source Code for Biology and Medicine* 2014; 9:14.

therefore becomes complex and inefficient. In efforts to standardize DEs to optimize registry use, update and aggregation, Bellgard *et al.* encourage the use of software that can be applied across different registries by all administrators. The authors propose constructing registries using several web framework programs and open source database systems. The aim is to design dynamic and user-friendly patient registries that do not require additional software development or professional assistance. Python (www.python.org) programming and MongoDB (www.mongodb.org) open-source document repository allow non-professional administrators to build efficient, dynamic and interrelated registries. Data coding programs such as YAML (www.yaml.org) also allow designers to import and export documents whenever necessary to complete information, such as patient consent, or share data with other research communities. Bellgard *et al.* believe these programs and features to enhance RDRF design will improve data mining, sharing and re-use across registries, essential to conduct research and clinical trials on rare diseases.

1.29. Crowdfunding campaign to support research

Alkaptonuria (AKU) was the first genetic disease to be discovered over 110 years ago. Besides the fact that AKU patients are often faced with misdiagnosis, a lack of efficient care and a lack of awareness, AKU still has no cure. The medical world remains largely unaware of its existence and impact on everyday life. Over 100 years later, the drug nitisinone has been identified as the first potential treatment for AKU. Nitisinone is already licensed as a treatment for another rare disease, but has not been approved to treat AKU. The first clinical trial was conducted in 2013 and AKU patients were subsequently recruited to participate in a second longitudinal trial. The four year trial to assess long-term nitisinone suitability for use in AKU patients was to begin at the end of 2013. Based at three test centers in Liverpool (UK) and in Paris (France), the study aims to recruit AKU patients scattered around the world. A crowdfunding campaign¹¹⁰, initiated by Nick Sireau –father of two boys with AKU, who quit his job to devote his time towards helping AKU patients– aims to generate funds for the clinical trial. The clinical trial needs 140 participants and although this number may seem small, it is often a challenge to reach these numbers in rare diseases. The campaign appealed to donors to raise funds to help identify and recruit patients worldwide.

1.30. Twitter to enroll patients in clinical research

“In a world in which excessive sharing of information is becoming increasingly normalised, maintenance of patient privacy has never been more important”, concludes a *Lancet Oncology*¹¹¹ editorial regarding the advantages and pitfalls of resorting to social media and crowdsourcing to recruit patients in clinical research. The more people ‘Google’, ‘Facebook’, ‘Tweet’ and ‘blog’ about rare diseases, the more they become aware of what is going on in the rare disease community. Besides enabling patients to become more informed, the author suggests that social media also allow individuals to play an increasingly active part in

¹¹⁰ Help cure Black Bone Disease. 25 April 2013 <http://vimeo.com/64796306>

¹¹¹ #trial: clinical research in the age of social media. *The Lancet Oncology* 2014; 15(6): 539.

their disease management, from diagnosis to clinical trial enrolment. By engaging in online communities, patients might also become more willing to take part in clinical trials. The article confirms that researchers do recruit patients directly through online patient support groups. In the US for instance, patients are able to sign up for clinical trials on the CureLauncher (www.curelauncher.com) website. To avoid bias however, patient anonymity is essential in clinical trials. But as patients continue to blog and exchange information online whilst enrolled in a clinical trial, they might inadvertently reveal their identity and clinical trial regimen to researchers, thus discrediting the purpose of blind studies. The author raises further questions concerning the protection of patient anonymity and patient data ownership in social networks. Typically, as patients become more informed and engaged, so do they face greater risks of overexposure and under-protection from misleading information or information they cannot interpret adequately. Rather than undermine social media however, the author recommends that clinicians take them into consideration when designing clinical trials.

1.31. The self-regulating orphan drug market: no concern for budget impact in the future

The introduction of the European Orphan Medicinal Product (OMP) Regulation¹¹² in 2000 prompted significant growth in OMP designations and marketing authorizations in Europe. By 2012, out of 878 OMP designations, 78 gained market access. According to DG Health & Consumers, these figures have reached 101 authorized OMPs for 1009 designations. According to a recent article in *Orphanet Journal of Rare Diseases*¹¹³, policy makers and payers in Europe are growing concerned about the potential consequent increase in OMP expenditure. The authors suggest that adopting strict pricing and reimbursement policies might not, however, be the answer. Findings from this comparative study of Sweden and France estimate that 152 OMPs will have received market authorization by 2020, for an average 146 annual new OMP designations. The article further suggests that the low OMP market approval rate, loss of intellectual property protection after twelve years and market exclusivity after ten years (resulting in 60-65 percent price cuts), will contribute towards curbing the impact of OMPs on health expenditure. The authors expect the OMP budget impact to remain sustainable from 2013 to 2020 (2.7 to 4.1 percent in Sweden and 3.2 to 4.9 percent in France), representing only a small proportion (4 to 5 percent) of total European pharmaceutical expenditure, in line with previous forecasts. Furthermore, only the top five selling OMPs in Sweden and France report sales above SEK 30 million (3.3 million Euros) and 50 million Euros, respectively. Along with a predicted budget impact reduction after 2018, the authors suggest that the growth in OMP numbers should not, therefore, be cause for concern.

¹¹² Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. *Official Journal of the European Communities*, 22 January 2000 <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32000R0141&from=EN>

¹¹³ Hutchings A *et al.*: Estimating the budget impact of orphan drugs in Sweden and France 2013–2020. *Orphanet Journal of Rare Diseases* 2014; 9: 22.

1.32. Synergy between Big Pharma and biotechs: the wave of the future

Biotechs have traditionally paved the way for innovation-led, indication-focused orphan drug development. They routinely “outperform multinational pharmaceuticals in the discovery and development of orphan medicines”. An article published in *Expert Opinion on Orphan Drugs*¹¹⁴ believes that Big Pharma is also trying to secure a position in this market through acquiring biotechs, generating new business units and co-developments. These developments, although slow, are essentially positive for patients as well as the industry. The author highlights how Big Pharma recognizes that the financial potential and fiscal benefits granted for orphan therapies are crucial to bring more orphan drugs to the market. The author believes that the pharmaceutical industry has had less impact on the orphan drug landscape at the discovery stage. Big pharma has contributed to the development of only one or two of the current best-selling orphan drugs (Glivec/Gleevec, Imatinib from Novartis and Tracleer from Roche). Nevertheless, biotechs –described as the 'child' of the orphan drug legislation– remain at the forefront of discovery and early clinical development of innovative technologies for orphan diseases. By providing examples of how orphan drugs are the new blockbusters, the author confirms that, though they cater for small populations, the commercial potential of orphan therapies outweighs the perceived barrier of small patient numbers. Although the author understands that Big Pharma is unlikely to be the main innovation engine for the next generation of orphan technologies, the move of multinationals into the rare disease space allows the rapid development of this sector as they provide access to development, manufacturing and marketing capacities required for new medicinal products.

1.33. Beyond economic considerations: Health Technology Assessment for rare diseases should incorporate multiple criteria

In an editorial published in *Expert Review of Pharmacoeconomics & Outcomes Research*¹¹⁵, Simoens defends the validity of Health Technology Assessment (HTA) using multi-criteria decision analysis to evaluate medicines and technologies for rare diseases. As he points out, HTA does in theory appear suitable to assess health products for rare diseases based on the European Network for Health Technology Assessment’s (EUnetHTA) definition of HTA: “Health technology assessment is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective health policies that are patient focused and seek to achieve best value”. In practice however, HTA is often and almost exclusively based on the cost-effectiveness of orphan products. In an article published earlier this year in the *Quarterly Journal of Medicine*¹¹⁶, Hyry *et al.* argue that orphan drugs usually do not meet efficiency

¹¹⁴ O’Neil DA: A better fit? Biotech versus Big Pharma in orphan/rare disease drug research. *Expert Opinion on Orphan Drugs* 2014; 2(4): 317-319.

¹¹⁵ Simoens S: Health technologies for rare diseases: does conventional HTA still apply? *Expert Review of Pharmacoeconomics & Outcomes Research* 2014; 14(3): 315-317.

¹¹⁶ Hyry *et al.*: Limits on use of health economic assessments for rare diseases. *Q J Med* 2014; 107:241–245

criteria under such conditions. Drummond *et al.* agree and add, in another article published in 2014 in *European Journal of Health Economics*¹¹⁷, that unless orphan drugs acquire ‘special’ status, policies to stimulate orphan drug development and policies to reimburse these medicines will continue to diverge. They suggest that increased collaboration between governments internationally, reflecting the global reach of pharmaceutical companies, might be part of the solution to reconcile these opposing policies. At a European level, EUnetHTA and EMA have in fact examined HTA policies in efforts to coordinate regulatory approval and reimbursement decisions. The outcome report of their joint initiative was announced in June¹¹⁸ and published in *Value in Health*¹¹⁹. The EMA and EUnetHTA continue to investigate ways of addressing regulatory obstacles early on in efforts to improve medicines and orphan product evaluation, based on multi-stakeholder and multidisciplinary criteria.

1.34. The need to build minimum and common data sets to research, diagnose and treat rare diseases more efficiently

In an article published in the *Journal of the American Medical Informatics Association*¹²⁰, Choquet *et al.* propose a methodology to establish standards for rare disease data collection. Based on a systematic review of the literature and the identification of data elements (DEs), the authors aim to establish homogeneous DEs common to all rare diseases, collect electronic health records at the bedside and promote the development of standardized European rare disease registries. The authors highlight the need for appropriate methodology and stakeholder consensus to establish common data elements (CDEs) in order to render data collected in clinical settings reusable for patient care, epidemiology and research. Since European countries have begun launching their national plans to advance rare disease research and treatment, the necessity and the difficulty to collect consistent and harmonized data sets on rare disorders has become all the more apparent. France’s first national plan on rare diseases (2005-2009)¹²¹ focused on groups of diseases and aimed to develop a network of rare disease centers and research units. France’s second national plan on rare diseases (2011-2014)¹²² funded information technology tools for these disease centers to develop a French minimum data set for rare diseases (F-MDS-RD). The F-MDS-RD builds on 42 CDEs and 16 national DEs. Presently, countries can use one of three coding systems for rare disease diagnosis, namely Orphanet, OMIM or SNOMED Clinical Terms, depending on the level of detail required. In France, investigators use Orphanet codes as the country has not acquired the license to use

¹¹⁷ Drummond M, Towse A: Orphan drugs policies: a suitable case for treatment. *The European Journal of Health Economics* 2014; 15(4): 335-340.

¹¹⁸ EMA: Outcome report on first European collaboration between regulators and HTA organisations: improving the contribution of regulatory assessment reports to health technology assessment. 25 June 2014
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2014/06/WC500169189.pdf

¹¹⁹ Berntgen M *et al.*: Improving the Contribution of Regulatory Assessment Reports to Health Technology Assessments—A Collaboration between the European Medicines Agency and the European network for Health Technology Assessment. *Value in Health* 2014; 17(5): 634-641.

¹²⁰ Choquet R *et al.*: A methodology for a minimum data set for rare diseases to support national centers of excellence for healthcare and research. *Journal of the American Informatics Association* 2014; [Epub ahead of print]

¹²¹ French Ministry of Health and Social Protection: French National Plan for Rare Diseases 2005-2008 “Ensuring equity in the access to diagnosis, treatment and provision of care”. 20 November 2004 http://www.sante.gouv.fr/IMG/pdf/French_National_Plan_for_Rare_Diseases.pdf

¹²² French Ministry of Social Affairs, Health and Women’s Rights: Plan national maladies rares 2011-2014: Qualité de la prise en charge, Recherche, Europe : une ambition renouvelée http://www.sante.gouv.fr/IMG/pdf/Plan_national_maladies_rares_2011-2014.pdf

SNOMED-CT coding. In the US, the Office of Rare Diseases Research (ORDR) national CDEs for rare diseases help collect homogeneous patient data into the Global Rare Diseases Patient Registry and Data Repository (GRDR). In the absence of a comprehensive international rare disease classification system, however, initiatives such as IRDiRC are hindered by incomplete data. In June 2013, the former EUCERD and EPIRARE recommended national rare disease data collection based on CDEs in order to harmonize, share and complement data among different databases, including Orphanet and the GRDR.

1.35. Ways to optimize bioinformatic tools to translate data into therapeutic development for rare diseases

Progress and innovation in rare disease (RD) treatment relies increasingly on advances in bioinformatics and international coordination of RD registries and biobanks. In an article published in *Health Policy and Technology*¹²³, Bellgard *et al.* identify a further seven components they believe must be standardized and harmonized to translate research on RDs into therapeutic opportunities: patient-practitioner partnerships, genomics platforms, population-wide studies, industry partnerships, personalized treatment, electronic health records and regulation. Bellgard *et al.* propose building on these initiatives to rationalize data collection activities. As RD registries expand internationally, the authors highlight the need to further develop common RD data elements and clinical data management systems to capture patient records dynamically. Practitioners, academia and the industry must respect international standards of common data elements and ontology, *i.e.* disease classification, to ensure accuracy of data used in research, disease natural history studies, population-wide studies, diagnostics and tailored medicine. The authors believe harmonizing registries and new technologies will facilitate collaboration between academia, industry, patient advocates and regulators. Such partnerships would attract increased funding and expertise on RDs, resulting in speedier therapeutic development.

1.36. Recommendations to improve efficiency of clinical trials for rare diseases

In an article published in *Best Practice & Research Clinical Rheumatology*¹²⁴, Beresford *et al.* review clinical trial methodologies developed to evaluate treatments for rare diseases. Since limited numbers of clinical trials are conducted on rare diseases, the authors suggest that sponsors must strive to produce results that benefit standards of care. They emphasize the need for rigorous clinical trial designs, adapted to rare conditions, in order to improve trial efficiency and obtain significant results in small patient pools. The authors further highlight the importance of selecting appropriate end points to measure clinical outcomes, relevant for clinical pathway decision making. As mentioned in *OrphaNews*¹²⁵, a number of clinical trials have been developed or adapted to best address rare diseases. Adaptive trials may

¹²³ Bellgard MI *et al.*: Rare Disease Research Roadmap: Navigating the bioinformatics and translational challenges for improved patient health outcomes. *Health Policy and Technology* 2014; Published Online: August 18 2014.

¹²⁴ Tudor Smith C, Williamson PR, Beresford MW: Methodology of clinical trials for rare diseases. *Best Practice & Research Clinical Rheumatology* 2014; 28(2): 247-262.

¹²⁵ Not just a number: The benefits of putting patients at the heart of clinical trials. *OrphaNews* 1 July 2014.

increase statistical significance and be more efficient in small patient groups. Participants act as their own control since their reaction to the different treatments may be assessed in short timeframes. Moreover, patients suffering from often life-threatening rare conditions are not exposed to long periods without treatment. Described in the EMA's Guideline on clinical trials in small populations¹²⁶, examples include response-adaptive, early escape, Bayesian, crossover or N-of-1 trials, in which participants receive one of two, or several, treatments sequentially. Nevertheless, Beresford *et al.* highlight several limitations to these trial designs. The long term effects of certain treatments in crossover and N-of-1 trials might hamper the analysis of study results. Furthermore, such trials might not produce significant results if the disease is fast evolving or in which relapse and remission periods are erratic. The authors recommend, therefore, that investigators conduct systematic reviews of the literature before designing or adapting clinical trials for rare disease treatments. The growing body of literature on rare disorders could help sponsors assess the disease natural history and mechanisms.

As collaborative initiatives increase in rare disease research, such as IRDiRC, the authors believe resources must also be pooled to harmonize clinical trial outcomes. One such project, the Core Outcome Measures in Effectiveness Trials (COMET, www.cometinitiative.org) initiative draws on researchers globally to develop core outcome sets (COSs)¹²⁷, i.e. *“the minimum that should be measured and reported in all clinical trials of a specific condition”*. Another research consortium, the EU-funded Integrated Design and Analysis of small population group trial (IDEAL, www.ideal.rwth-aachen.de) project investigates new methods of design and analysis for clinical trials in small participant pools. The project aims to generate clinical trial methodologies better adapted to rare diseases.

1.37. A study of the literature shows high interest for rare disease and orphan drug research

A scientometric review—or ‘quantitative study of scientific literature’—, provides insight into the areas of greatest interest concerning research on specific topics. In an article published in *Expert Opinion on Orphan Drugs*¹²⁸, Chen *et al.* review the scientific literature on orphan drugs and rare diseases in order to establish research trends in these fields. The authors used an analytic tool (CiteSpace) to visualize patterns in the scientific literature. The aim of this study was to complement expert reviews on trends in research on orphan drugs and rare diseases. The authors collected publication data from Web of Science. Based on a core dataset of 7,753 records published between 2000 and 2014 on orphan drugs, the authors investigated the frequency at which these records were cited in some 76,897 further publications. They discovered several *“citation bursts”*, reflecting specific attention to a

¹²⁶ EMA: Committee for Medicinal Products for Human Use (CHMP) Guidelines on Clinical Trials in Small Populations. 27 July 2006 http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003615.pdf

¹²⁷ Williamson PR *et al.*: Developing core outcome sets for clinical trials: issues to consider. *Trials* 2012; 13: 132.

¹²⁸ Chen C, Dubin R, Chul Kim M: Orphan drugs and rare diseases: a scientometric review (2000 – 2014). *Expert Opinion on Orphan Drugs* 2014; 2(7): 709-724.

topic, thus suggesting increased focus on particular areas of interest within rare diseases and orphan drugs. Citation bursts in this review highlight correlations between common and rare diseases, focus on clinical trials for orphan drugs, value of health technology assessment for orphan medicines and industrial development of orphan medicinal products. Keywords were also examined to illustrate trends in research. The authors discovered that, since 2000, some of the most frequently cited keywords include *Crohn's disease*, *single-nucleotide polymorphisms* and *genome-wide association*. Through this scientometric review, the authors identify three areas of interest concerning rare diseases and orphan drugs: research policy, basic research and clinical research. They believe the literature reveals a lack of translational research in the field of rare diseases and orphan drugs. The authors therefore recommend that further studies be conducted on linking basic research to clinical and therapeutic development. They also recommend that further research be conducted on studies associating common and rare diseases.

1.38. Data protection goes too far in Europe

The European Parliament's rapporteur on the Data Protection Regulation published a draft report¹²⁹ recommending that *"...processing of sensitive data for historical, statistical and scientific research purposes is not as urgent or compelling as public health or social protection"*. This report is a cause for concern as enacting it into law may make recruiting subjects for clinical research through registries extremely difficult. Although it includes an amendment allowing data use after obtaining informed consent, it may restrict registry-based research, which has provided valuable insights in the field of rare disease research. Another amendment in the report allows the passing of a law permitting the use of pseudonymized/key-coded data without consent in cases of "exceptionally high public interest". However, garnering public interest for rare disease research can be challenging. Furthermore, using pseudonymized data will be a major setback for several research collaborations that are trying to make optimal use of scarce resources and data available to them. Although rare disease patients have privacy concerns, one of the biggest challenges they face is the insufficient or in most cases lack of treatment options available to them. Many patient groups are advocates of disease registries and databases and have helped initiate their development with medical experts in efforts to further research and development of treatment options. The significance of the right to proper treatment for rare disease patients cannot be undermined. Thus a delicate balance must be observed, particularly for rare disease patients.

¹²⁹ Albrecht JP: Draft Report on the proposal for a regulation of the European Parliament and of the Council on the protection of individual with regard to the processing of personal data and on the free movement of such data. *European Parliament, Committee on Civil Liberties, Justice and Home Affairs* 17 December 2012 http://www.europarl.europa.eu/meetdocs/2009_2014/documents/libe/pr/922/922387/922387en.pdf

1.39. Key Figures in Rare Disease research express concern over the European Reform of the Data Protection Rules (RoDPR)

In a 2013 comment published in the Ethics watch section of *Nature Reviews Genetics*¹³⁰ researchers and clinicians of the rare disease community expressed concern over the proposal to revise privacy laws in Europe. The authors do not favor the proposal's aim to treat personal information use in rare disease research and "regulating commerce or the Internet" identically. The authors believe that provisions of the current privacy laws, allowing data-sharing if they are codified and confidentiality is guaranteed, will be withdrawn if the amendments proposed by the Committee on Civil Liberties, Justice and Home affairs and the European Reform of the Data Protection Rules (RoDPR) are followed through. A considerable amount of research on rare disease depends on access to data from biobanks and registries. The authors point to the fact that the European Commission requires Member States to develop registries as part of their rare disease national plans. They emphasize that to use data provided in these registries, there must be some degree of openness regarding data sharing. Data sharing becomes especially important for rare disease research because of the need to cross national borders to increase rare disease patient sample sizes. The article highlights that Article 8 of the Charter of Fundamental Rights of the EU, recognizing the rights to protection of personal data, is not an absolute right. In fact most of the rights provided by the Charter are not absolute and according to the authors "should be balanced with other rights" in addition to society's collective rights, such as the right to quality medical treatment and the right of integration of persons with disabilities. The authors highlight that the rare disease community, including researchers, clinicians and patient organizations, have expressed deep concern regarding these amendments and oppose this modification in privacy laws.

1.40. When is patient data protection too much or too little protection?

Research on rare diseases is challenging due to the typically limited number of cases, and therefore depends heavily on international registries and patient data sharing. Despite countries adopting regulations to protect patient identity in research, progress in genetics and data pooling have increased the possibility of identifying individuals in research cohorts. Furthermore, according to a systematic review, published in the journal of *Applied & Translational Genomics*¹³¹, the various consent models - broad consent, de-identification, re-consent - appear not to have achieved the much needed balance between keeping patients informed and fostering research. The authors highlight that regulation must, therefore, satisfy the need to protect patient integrity and enable research to progress and lead to the development of targeted therapies for rare disease patients. The review observes that rare disease patient associations do recognize the importance of advancing research, which itself relies heavily on patient trust and information. The authors suggest that patients should,

¹³⁰ Mascalzoni D *et al.*: Rare diseases and now rare data? *Nature Reviews Genetics* 2013; 14(372).

¹³¹ Mascalzonia D, Paradiso A, Hansson M: Rare disease research: Breaking the privacy barrier. *Applied & Translational Genomics* 2014; 3(2): 23-29.

therefore, become active partners in research on rare disorders, through dynamic consent models, such as participant centric interfaces (PCI) and thick opt-out strategies, in order to both protect their interests and support research.

1.41. The online financial services company Motley Fool encourages investment in orphan drugs and orphan drug developers.

According to a *Thomson Reuters* study¹³², the past decade has shown an exponential growth in revenue for orphan drugs compared with non-orphan drugs. The average approval time is 3.5 years for orphan drugs and 5 years or more for non-orphan drugs. The lack of strong competition, due to the seven year exclusivity clause and the small number of manufacturers involved in development, is a further source of orphan drug market success. Annual cost per patient for recently approved drugs, such as Juxtapid, Gattex or Elaprase, is at least US\$300,000. On the downside, some orphan drugs may not be reimbursed which prevents access to treatment for a number of patients. Motley Fool encourages investment in orphan drugs as well as buying stock options in companies that develop orphan drugs.

1.42. The benefits of putting patients at the heart of clinical trials

The authors of an article published in *Value for Health*¹³³ regret that classical clinical trials generally do not represent patient interests and rarely inform participants of results during the study. Under such conditions, patients often lose interest and drop out of trials. Experience shows that participants' active involvement in the design and progression of clinical trials results in greater patient retention and more meaningful results. Informed patients are more willing to engage in time-consuming and effort-requiring studies as they feel valued, empowered and capable of assessing therapeutic options. Mullins *et al.* suggest methods of designing trials from a patient's point of view rather than the investigator's. Pragmatic, Bayesian statistics and adaptive trials can improve patient safety and increase recruitment and retention. Pragmatic trials are designed to result in outcomes that are most relevant and beneficial to participants. Bayesian statistics draw on collected evidence to update knowledge on the treatment and outcome probabilities. This approach aims to produce results that are easily interpreted and reflect the reality of medical decision making. Adaptive trials also evolve on the basis of data accumulated during the trial and allow patients to be transferred to a more effective treatment if it becomes available once the trial has begun. The three trial designs are particularly relevant for rare diseases as they are more likely to retain already limited numbers of patients, whilst potentially offering them early benefits. Nevertheless, the authors highlight several limitations: pragmatic trials are designed to reflect a 'real world' situation which is difficult to quantify and qualify; Bayesian statistics are resource intensive; and adaptive trials might not offer the required evidence for regulatory approval. To truly qualify trial designs as patient-centered, Mullins *et al.*

¹³² The Economic Power of Orphan Drugs. *Thomson Reuters* 2012.

¹³³ Mullins CD *et al.*: Patient-Centeredness in the Design of Clinical Trials. *Value in Health* 2014; 17(4): 471-475.

emphasize the primary need for sustained efforts to inform and involve patients and advocates at all stages of clinical studies.

1.43. Early escape crossover trials for rare diseases are better adapted to patient needs and preferences

A clinical research report published in *Contemporary Clinical Trials*¹³⁴ illustrates the advantages of adaptive trial designs for rare diseases. Adaptive crossover trial designs, giving patients the option to opt out or 'escape' the assigned treatment, can improve outcome efficiency and statistical significance. Increasingly designed to investigate new treatments for rare diseases, crossover trials involve two or more treatments administered in a set order to each patient and for set periods throughout the study. Patient 1 will receive treatment A followed by treatment B, whilst Patient 2 will receive treatment B followed by treatment A for the same period. Crossover trials therefore minimize patient exposure to ineffective treatments and increase efficiency since patients act as their own control and response to treatment is rapidly measured. A randomized, double-blinded, placebo controlled crossover trial was designed to test a new treatment for Familial Mediterranean Fever (FMF), a rare genetic autoinflammatory disorder, characterized by recurring fever attacks. Patients received one of four treatment sequences alternating riloncept (R) and placebo (P): RPRP, PRPR, RPPR and PRRP. Patients who experienced at least two FMF attacks during one course of treatment were allowed to escape to the other treatment arm until the end of that course. Participants then resumed the assigned treatment sequence. The investigators indicate that escape options helped reduce patient dropout from clinical trials and, contrary to Mullins *et al.*'s views mentioned in the previous article, increased study efficiency and significance. Where clinical trials for rare disease treatments are challenging, typically due to small patient numbers, crossover trials with early escape options increase patient motivation, minimize adverse effects, maximize treatment benefits and improve the significance of collected data.

1.44. Megafunds to finance orphan drug discovery: a new approach

In the face of pharmaceutical industry productivity decline over the past several years, the authors of an article published in *Drug Discovery Today*¹³⁵ propose a novel method of financing drug discovery. Fagnan *et al.* introduce the concept of 'megafunds' to attract investments into risky orphan drug research and development projects. A megafund would raise funds by issuing 'research-backed obligations' (RBOs), *i.e.* bonds on potential revenues from future sales of orphan drugs and intellectual property. Instead of relying on venture capitalists and other investment funds, megafunds could attract capital into orphan drug portfolios from a much larger investor base, usually unable to invest in early-stage drug discovery. Based on their simulations and the assumption of high success rates, the authors

¹³⁴ Huang B *et al.*: Enhancing crossover trial design for rare diseases: limiting ineffective exposure and increasing study power by enabling patient choice to escape early. *Contemporary Clinical Trials* 2014; 38(2): 204-12.

¹³⁵ Fagnan D *et al.*: Financing drug discovery for orphan diseases. *Drug Discovery Today* 2014; 19(5): 533-538.

suggest that megafund portfolios containing ten to twenty investigational compounds could deliver potentially, albeit uncertain, high returns on investment. While Fagnan *et al.* admit their simulations are only indicative of megafund potential, they maintain that novel financing models, such as RBOs to constitute megafunds, should be developed to address growing drug discovery challenges. By pooling and diversifying resources, the authors believe that megafunds spread their risk and offer greater financial flexibility whilst ensuring more efficiency and lower drug development costs.

1.45. Graph Theory enables Drug Repurposing by driving the discovery of hidden mechanisms of action

In an article published in *PLoS One*¹³⁶, the authors describe how Graph Theory methodology allows investigators to efficiently exploit natural-language expressed biomedical knowledge to repurpose existing drugs to treat diseases for which they were not initially intended. The method consists in building a graph representation of knowledge which is automatically analyzed to discover hidden relations between any drug and any disease. These relations are specific paths between the biomedical entities of the graph and represent potential modes of action for any given pharmacological compound. Applications of this methodology for rare diseases are promising.

2. Trends in the field of diagnostics development

2.1. European Genome-Phenome Archive

In May 2012, the Pediatric Cancer Genome Project (PCGP, www.pediatriccancergenomeproject.org) announced the release of a comprehensive human cancer genome data, freely accessible by the global scientific community. The data is available in the European Genome-phenome Archive (www.ebi.ac.uk/ega/home), an online repository that allows researchers to explore datasets from numerous genotype experiments, supplied by a range of data providers. Since 2012, the Genome-phenome Archive has widened data collection to other disease types and therapeutic fields.

2.2. FindZebra

In an article published in the *International Journal of Medical Informatics*¹³⁷, the authors describe the work of Danish researchers who have built FindZebra (findzebra.compute.dtu.dk) a search engine designed exclusively for medical professionals to diagnose rare diseases. FindZebra is an open-source search technology using curated, freely available medical information from sources such as the Online Mendelian Inheritance in Man database (OMIM), the Genetic and Rare Diseases Information Center and Orphanet. The layout of this website is simple, much like Google, with a search bar and basic information on

¹³⁶ Gramatica R *et al.* : Graph Theory Enables Drug Repurposing – How a Mathematical Model Can Drive the Discovery of Hidden Mechanisms of Action. *PLoS ONE* 2014; 9(1): e84912.

¹³⁷ Dragusin R. *et al.* : FindZebra: A search engine for rare diseases. *International Journal of Medical Informatics* 2013; 82(6): 528-538.

the site. Entering a patient phenotype query, for instance ‘flat nose, cleft palate, protineuria’, into the search bar will return twenty search results in decreasing order of relevance.

2.3. Cafe Variome

Internet-based Cafe Variome (www.cafevariome.org), launched in 2011, is designed to function as a clearinghouse and exchange portal for gene variant (mutation) data produced by diagnostic laboratories. Cafe Variome acts as a universal data reception and advertisement point, offering users a secure environment through which to announce, discover and acquire a comprehensive listing of observed neutral and disease-causing gene variants in patients and unaffected individuals. Each variant in Cafe Variome will be accompanied by basic phenotypic annotation. To achieve this, Cafe Variome facilitates the publication of data from researchers, diagnostics laboratories and other sources. Data may be used by all stakeholders wishing to analyze the evidence of causal influence upon certain disease states and/or incorporate the data into locus-specific databases (LSDBs). While data generators generally do not object to disseminating anonymized diagnostic data, they are also not motivated to do so because of the effort and time involved. Furthermore, they would not want to send the data to several destinations with differing submission requirements. Cafe Variome specifically addresses these issues by:

- ▶ Enabling data analysis tools used by research and diagnostic laboratories with a ‘data submission’ function which automatically pushes diagnostic data in a standardized format into Cafe Variome;
- ▶ Working closely with providers of variant interpretation software used in diagnostic laboratories to produce versions of these tools that allow users to submit sequence variants directly to Cafe Variome;
- ▶ Offering manual support to laboratories to move their variant datasets into Cafe Variome (legacy data and new data in batches or in real time);
- ▶ Providing a single depot which can be conveniently searched to identify newly discovered variants in genes of interest, making them available for controlled- or open-download by diverse third parties;
- ▶ Ensuring total control by the data submitters, over who may and may not access their data, through a convenient system for granting access rights where appropriate;

The development of Cafe Variome (based at the University of Leicester, UK) involves the cooperation of diagnostic software companies PhenoSystems (Gensearch) and Interactive Biosoftware (Alamut) as well as academic partners in the Bioinformatics Support Group at Leiden University Medical Centre (LUMC), whose Mutalyzer data-validation tool will permit feedbacking data-inconsistencies to submitters, and at NGRL Manchester who have extensive expertise in diagnostic databases through their development of DMuDB.

Key data suppliers who have already deposited data into Cafe Variome include: Pilot data from four diagnostic laboratories (University of Würzburg, Germany; Hôpital Ambroise Paré, Paris; Liverpool Women's Hospital, UK; Instituto de Genética Médica Jacinto Magalhães, Portugal); HGMD; dbSNP; UniProt; and PhenCode. Cafe Variome is part of the GEN2PHEN project which receives funding from the European Community's Seventh Framework Programme under grant 200754. GEN2PHEN has the global objective of unifying human and model organism genetic variation databases towards increasingly holistic views into Genotype-To-Phenotype (G2P) data by establishing data standards and exchange protocols. The ultimate goal is to link biomedical knowledge sources in a seamless fashion. Access to all of Cafe Variome facilities is free of charge.

V. THERAPEUTIC BREAKTHROUGHS

1. Approved therapeutic innovations

1.1. Retinal implant approved by FDA for patients suffering from retinitis pigmentosa

In 2013, the Food and Drug Administration (FDA) approved Second Sight's Argus II Retinal Prosthesis System for the treatment of advanced retinitis pigmentosa (RP)¹³⁸. RP is a debilitating rare genetic disease that affects about one in 4,000 people in the US and about 1.5 million people worldwide. The retina's photoreceptors, the rod and cone cells convert light into electrical signals transmitted via the optic nerve to the brain's visual cortex for processing. In patients suffering from RP, these light sensitive cells die due to an unknown mechanism, leading to blindness in advanced stages. The retinal implant does not restore vision completely but *"allows (the patient) to detect light and dark in the environment"* and thus perceive images and movement. The Argus II consists of a small video camera, a transmitter mounted on a pair of eyeglasses, a video processing unit and a 60-electrode implanted retinal prosthesis that replaces the function of the dead cells in the retina. The video processing unit transforms images from the video camera into electronic data that is then transmitted to the retinal prosthesis. This device received a unanimous approval by the FDA's Ophthalmic Devices Advisory Panel in September 2012. The developers plan to use this technology to accommodate patients suffering from age-related macular degeneration, a similar but more common condition. Competition, however, is not far behind, as many companies are building similar *'bionic eyes'* using different technologies.

2. Potential of therapeutic innovations

2.1. Pluripotent stem cells in regenerative medicine: the road ahead

The potential of pluripotent stem cells (hPSC) as unlimited sources of disease-relevant cell types has led to several research efforts gaining significant preclinical evidence. Bringing hPSCs from bench to bedside is becoming an increasingly realistic prospect. However, the preparedness of academia and the industry for this eventuality is not certain. In an article published in *Nature Genetics Reviews*¹³⁹, the authors describe the potential clinical translation of stem cell treatments and the challenges of bringing such therapies to the market. Improved protocols are now available for directed differentiation, resulting in new technologies that facilitate deriving therapeutically relevant cell types from hPSC sources. The authors highlight recent therapeutic development breakthroughs for many cell lineages with neural and non-neural identities. Despite roadblocks and challenges, the authors described the tools to facilitate differentiation processes. They highlight progress made in

¹³⁸ FDA News Release: FDA approves first retinal implant for adults with rare genetic eye disease. 14 February 2013
<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm339824.htm>

¹³⁹ Tabar V, Studer L: Pluripotent stem cells in regenerative medicine: challenges and recent progress. *Nature Reviews Genetics* 2014; 15(2): 82-92.

directed differentiation through transcriptional programming, as well as in-vitro and imaging technologies to ensure hPSCs differentiate into the intended cells. The authors highlight the importance of validating robustness in relevant disease models and develop a cell-manufacturing strategy that is suitable for clinical translation. Important steps include producing cells on a sufficient scale (*i.e.* creating a cell bank) and using fully standardized protocols under current good manufacturing practice (GMP)-compliant conditions. Cell banks must be re-validated for safety and efficacy before cells can be considered as candidate clinical products for early safety studies, and eventually efficacy studies, in humans.

2.2. RNAi lost and found in translation: a breakthrough therapeutic area

*Nature Biotechnology*¹⁴⁰ reported on industry's progress to understand the benefits of RNAi as a potential treatment method of certain rare diseases. RNAi is part of the 'gene silencing' technology, whereby small RNA strands (20-24 base pairs) bind to complementary RNA *in vivo*, forming a double-stranded RNA, preventing the protein formation from that RNA. While this methodology has been successfully tried and tested in fundamental research, it has not been adopted into clinical research. The author describes how start-ups developed therapeutic platforms using this technology and how big pharma attempted to follow suit unsuccessfully. Nevertheless, initial setbacks were overcome following Alnylam's success using RNAi to treat patients suffering from rare liver diseases. Genzyme is thought to now covet Alnylam and would facilitate the therapy's development and marketing process. The author suggests that advances in methodologies to research and develop treatments for rare diseases, by looking beyond conventional drugs, pave the way towards innovative therapies. *"Companies pursuing gene therapy, gene editing and protein misfolding correction, to name a few, are reminding investors of what it was like in the genomics era, to dare to imagine transformative advances"*.

2.3. The promises of stem cell therapy: the EndoStem program for congenital muscular dystrophies

Launched in 2010, the EU co-funded EndoStem 7th Framework Programme¹⁴¹ is bearing its stem cells. The fifteen-strong partnership, coordinated by Professor David Sassoon and composed of academic institutes, biotechs and pharmaceutical companies, pooled resources to develop new ways of stimulating stem cells in rare muscle disorders. The consortium investigates innovative methods to reproduce physiological signals, associating skeletal muscle, vessels, the immune system and stem cells, to promote self-repair in damaged muscle tissue. This research holds great promise for the treatment of muscular dystrophies. Clinical trials, based on four different pharmacological approaches, are being conducted to mobilize endogenous stem cells in damaged muscle tissue. The research offers potential for

¹⁴⁰ Bouchie A: Markets, venture investors and big pharma interest in RNAi soars. *Nature Biotechnology* 2014; 32: 203-204.

¹⁴¹ European Commission: Stem cells: the key to tackling degenerative muscle disease. Community Research and Development Information Service (CORDIS) http://cordis.europa.eu/news/rcn/36548_en.pdf

translation into innovative and high-precision biopharmaceuticals. The project, due for completion by the beginning of 2015, brings new hope to patients suffering from congenital muscular dystrophies and other rare diseases, as well as more common degenerative disorders.



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